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Review – Prostate Cancer

Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology

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Abstract

Context: Introduction of novel agents for the management of advanced prostate cancer provides a range of treatment options with notable benefits for men with metastatic castration-resistant prostate cancer (mCRPC). At the same time, understanding of optimal patient selection, effective sequential use, and development of resistance patterns remains incomplete.
Objective: To review current systemic therapies and recent advances in drug development for mCRPC and strategies to aid in patient selection and optimal sequencing.
Evidence acquisition: A literature review of PubMed/Medline, Cochrane Library, Current Contents Medicine, Web of Science, Clinical Trial.Gov, WHO-ICTRP (January 2004–November 2017), and the proceedings of major international meetings (2015/2016/2017) was performed in November 2017.
Evidence synthesis: In the last few years, several new options for treatment of mCRPC have shown a survival benefit in phase III trials besides docetaxel:abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T. Radium-223 and denosumab have increased options in management of bone metastases. Currently, novel agents such as next-generation androgen receptor (AR) axis-targeting treatments, immunotherapeutics, or therapies targeting other oncogenic and genomic pathways, particularly poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors and PD-1 inhibitors, are under clinical investigation. With increasing treatment options for mCRPC, information on how to personalize management and how to select and sequence existing therapies is

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beginning to emerge, as are predictive biomarkers (homologous repair mutations, mismatch repair mutations, AR splice variant 7). Finally, early use of active agents in the castration-sensitive state will likely also change the clinical management of the disease when it becomes castrate resistant.

Conclusions: The emergence of new drugs for mCRPC has improved treatment options dramatically. Currently, systemic treatment options for mCRPC include hormonal therapy, chemotherapy, immunotherapy, and radionuclide therapy as well as bone-modifying agents and palliative or supportive measures. Further, new genetically targeted agents (PARP inhibitors and PD-1 inhibitors) are on the horizon for certain subsets of biomarker-selected patients. The best strategies for patient selection and optimal sequential use to achieve the longest cumulative survival improvement and to prevent early resistance remain unclear.

Patient summary: The current literature and proceedings from relevant congresses related to available systemic agents for the treatment of metastatic castration-resistant prostate cancer, including novel genetically targeted therapies, including poly(adenosine diphosphate–ribose) polymerase inhibitors and PD-1 inhibitors, were reviewed. Current therapies and ongoing developments are discussed.

1. Introduction

In the last few years, several new options for the treatment of metastatic castration-resistant prostate cancer (mCRPC) have been approved: the CYP17 inhibitor abiraterone, the androgen receptor (AR) antagonist enzalutamide, the taxane cabazitaxel, the immunotherapy sipuleucel-T, and the alpha-emitter radium-223 for men with bone metastases. All these therapeutic agents have proven survival benefit for mCRPC in clinical phase III studies. Until the beginning of the 2010s, docetaxel as a member of the taxane drug class had been the only life-prolonging agent for mCRPC [1]. Many other agents targeting AR signaling are currently being evaluated in clinical trials (Table 1).

This review provides an up-to-date summary of current therapies for the management of mCRPC. We focus on recently approved agents and emerging novel agents, and on how to choose which agent and how to sequence current agents in the context of potential development of cross resistance.

2. Evidence acquisition

The electronic database Medline (through PubMed) was searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in November 2017 to identify preclinical studies, clinical randomized controlled trials, and other relevant publications such as review articles, editorials, and letter to the editor (Fig. 1). In addition, abstracts from major international oncology conferences (ESMO and ASCO) from 2015 to 2017 were searched for relevant abstracts. The search terms included *castration resistant prostate cancer, clinical randomized controlled trial, docetaxel, abiraterone, enzalutamide, cabazitaxel, androgen deprivation therapy, radium-223, sipuleucel-T, novel agents*, and *chemotherapy*. ClinicalTrials.gov and WHO-ICTRP were assessed for information about ongoing clinical trials.

In addition, each author's knowledge of the current literature was used to ensure an adequate final literature review and selection.

3. Evidence synthesis

3.1. AR-targeted therapy

Despite the initially high response rate to androgen deprivation therapy (ADT), the majority of prostate cancers (PCs) will develop castration resistance inevitably over time, mostly within the 1st year of ADT in men with metastatic disease [2–4]. Addition of other treatments targeting androgen action may interrupt androgen axis signaling. Nevertheless, mCRPC tumors almost always acquire additional androgen-pathway resistance to second-generation hormonal therapies.

Multiple mechanisms underlie progression to the castration-resistant state: increased androgen biosynthesis in the tumor microenvironment or use of adrenal androgen precursors, and alterations of AR signaling including AR mutations, especially in the ligand-binding domain, for example, broader ligand specificity, AR variants that are constitutively active in absence of ligand, AR gene amplifications and overexpression, crosstalk with other signaling pathways, or reliance on non-AR–mediated pathways [3]. According to the current European Association of Urology guideline, castration resistance is defined by biochemical progression (three consecutive rises in prostate-specific antigen [PSA] 1 wk apart resulting in two 50% increases over the nadir, with PSA $>$2 ng/ml) or radiological progression (appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST 1.1) in the presence of serum testosterone $<$50 ng/dl or 1.7 nmol/l [2]. This definition is similar to the former PCWG2 criteria from 2008 [5], which were replaced by the PCWG3 criteria published in 2016 by Scher et al [6].

However, the AR pathway is often found to still be activated in mCRPC. Thus, AR signaling remains a target of

Table 1 – Current therapies in mCRPC

AR-targeted therapy		
Abiraterone	CYP17A1 inhibitor	Approved
Enzalutamide	AR antagonist	Approved
Orteronel (TAK-700)	CYP17A1 inhibitor	Under clinical evaluation
Seviteronel (VT-464)	CYP17A1 inhibitor	Under clinical evaluation
Apalutamide (ARN-509)	AR antagonist	Under clinical evaluation
Darolutamide (ODM-201)	AR antagonist	Under clinical evaluation
Chemotherapy		
Docetaxel	Taxane	Approved
Cabazitaxel	Taxane	Approved
Immunotherapy		
Sipuleucel-T	Therapeutic vaccine	Approved
PROSTVAC-VF	Therapeutic vaccine	Under clinical evaluation
Ipilimumab (MDX-010)	CTLA-4 inhibitor	Under clinical evaluation
Nivolumab	PD-1 inhibitor	Under clinical evaluation
Pembrolizumab	PD-1 inhibitor	Under clinical evaluation
Atezolizumab	PD-L1 inhibitor	Under clinical evaluation
Avelumab	PD-L1 inhibitor	Under clinical evaluation
Bone-targeted therapy		
Bisphosphonates		Approved
Denosumab	RANKL inhibitor	Approved
Radium-223	Radionuclide	Approved
PARP inhibitors		
Olaparib	PARP inhibitor	Under clinical evaluation
Veliparib	PARP inhibitor	Under clinical evaluation
Rucaparib	PARP inhibitor	Under clinical evaluation
Niraparib	PARP inhibitor	Under clinical evaluation
Talazoparib	PARP inhibitor	Under clinical evaluation
Other emerging therapies and novel therapeutic targets		
Selinexor	XPO-1 inhibitor	Under clinical evaluation
SM88	Agent combination	Under clinical evaluation
Cabozantinib	Tyrosine kinase inhibitor	Under clinical evaluation
Tasquinimod	Small-molecule inhibitor	Negative
^{177}Lu-PSMA-617	PSMA-targeted therapies	Under clinical evaluation

AR = androgen receptor; mCRPC = metastatic castration-resistant prostate cancer; PARP = poly(adenosine diphosphate–ribose) polymerase; PSMA = prostate-specific membrane antigen; RANKL = receptor activator of nuclear factor κB ligand.

therapeutic strategies upon the development of mCRPC. Therapeutic strategies for mCRPC have all been tested in combination with ongoing medical (ADT) or surgical castration, which should be continued in the castration-resistant state indefinitely, although pharmacokinetics may be altered negatively and increased clearance of docetaxel has been described in castrated men [7].

3.1.1. *Suppression of androgen biosynthesis*

Abiraterone acetate is an inhibitor of CYP17A1 and targets both 17α-hydroxylase and 17,20-lyase activities, thereby inhibiting residual androgen biosynthesis. Abiraterone was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of men with mCRPC after docetaxel chemotherapy in 2011 and men with mCRPC without previous chemotherapy in 2013 [8–10]. In the final analysis of the large randomized trial COU-AA-301, abiraterone prolonged overall survival (OS; 15.8 mo [95% confidence interval {CI} 14.8–17.0] vs 11.2 mo [10.4–13.1]; hazard ratio [HR] 0.74; 95% CI 0.64–0.86; $p < 0.0001$) at a median follow-up of 20.2 mo (interquartile range 18.4–22.1) in docetaxel-treated men with mCRPC when compared with placebo [8]. Abiraterone also improved all secondary endpoints, including time to PSA progression (10.2 vs 6.6 mo; $p < 0.001$), progression-free survival (5.6 vs 3.6 mo; $p < 0.001$), and PSA response rate (29% vs 6%; $p < 0.001$). In chemo-naïve asymptomatic or mildly symptomatic mCRPC patients, abiraterone improved radiographic progression-free survival, and delayed clinical decline and initiation of chemotherapy compared with placebo (COU-AA-302) [9]. In the final overall analysis at a median follow-up of 49.2 mo, median OS was significantly longer in the abiraterone acetate group than in the placebo group (34.7 mo [95% CI 32.7–36.8] vs 30.3 mo [28.7–33.3]; HR 0.81 [95% CI 0.70–0.93]; $p = 0.0033$) [11].

Concurrent administration of low-dose prednisone (5 mg twice a day) with abiraterone is required to prevent hypertension, hypokalemia, and fluid retention resulting from adrenocorticotropic-generated mineralocorticoid excess. In addition, monthly monitoring of liver enzymes is required.

Recently, results from the LATITUDE and STAMPEDE trials showed increased OS in men with locally advanced or hormone-sensitive metastatic PC when adding abiraterone to ADT [12,13]. James et al [12] reported about a 37% reduction in deaths in M0 and M1 patients treated with abiraterone and castration as compared with standard of care ADT-alone group (HR 0.63; 95% CI 0.52–0.76; $p < 0.001$) in the STAMPEDE trial. Fizazi et al [13] reported significantly longer median OS (not reached vs 34.7 mo; HR for death 0.62; 95% CI 0.51–0.76; $p < 0.001$) in high-risk metastatic castration-sensitive PC after a median follow-up of 30.4 mo in the LATITUDE trial. These data will change clinical practice and will also impact sequencing in mCRPC.

3.1.2. *AR blockade*

Second-generation AR antagonists are potent AR inhibitors with no significant activity in the setting of AR overexpression. Antagonist-to-agonist conversion is less common in these agents than in first-generation AR inhibitors such as bicalutamide.

Enzalutamide is a second-generation, nonsteroidal AR inhibitor that affects the AR pathway in three ways: it binds to the AR with greater relative affinity than bicalutamide, reduces the efficiency of AR nuclear translocation, and impairs both DNA binding to androgen response elements and recruitment of coactivators [14]. In the phase III AFFIRM trial, 1199 men with mCRPC progressing after chemotherapy were randomly assigned in a 2:1 ratio to receive oral enzalutamide 160 mg/d ($n = 800$) or placebo ($n = 399$) [15].

At a preplanned interim analysis after 520 deaths and a median follow-up of 14.4 mo, median OS was 18.4 mo (95% CI 17.3—not yet reached) in the enzalutamide group versus 13.6 mo (95% CI 11.3–15.8) in the placebo group (HR for death in the enzalutamide group 0.63; 95% CI 0.53–0.75; $p < 0.001$). Enzalutamide improved all the secondary endpoints of this placebo-controlled trial [15,16].

Similar to abiraterone, enzalutamide was also evaluated in chemo-naïve asymptomatic or mildly symptomatic mCRPC patients [17]. The PREVAIL study showed a

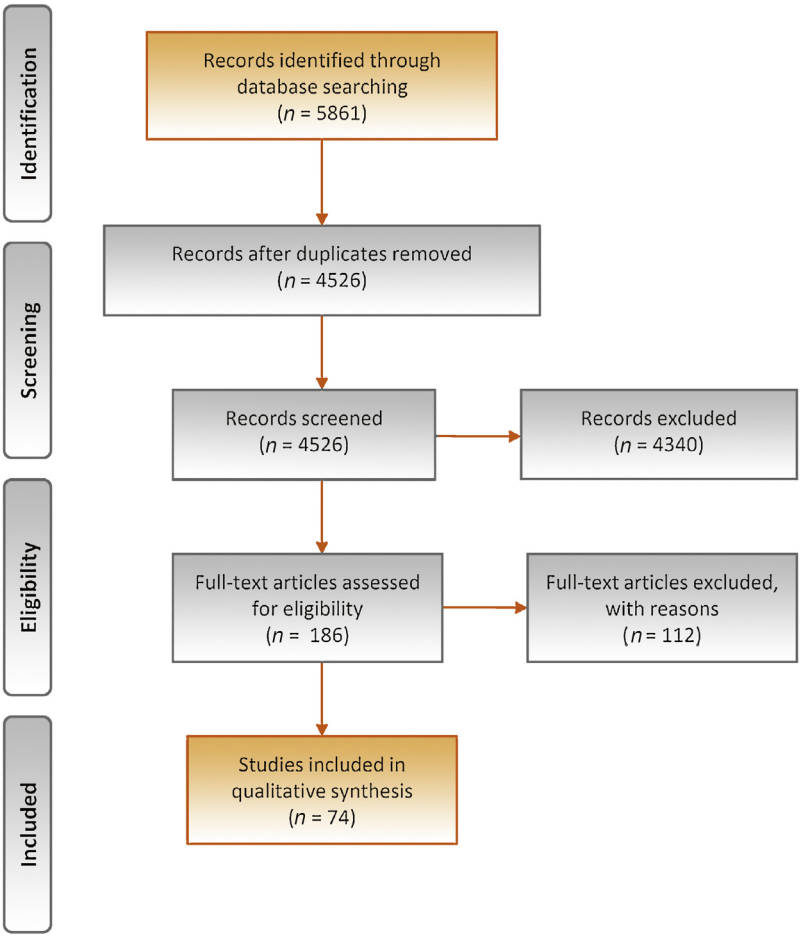

Fig. 1 – PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

significant decrease in the risk of radiological progression (81% risk reduction; HR in the enzalutamide group [n = 626] 0.19; 95% CI 0.15–0.23; $p < 0.001$) and a significant improvement in OS (29% reduction in the risk of death; HR 0.71; 95% CI 0.60–0.84; $p < 0.001$) compared with the placebo group (n = 532) [17]. At the final analysis, median OS was 35.3 mo (95% CI 32.2–not yet reached) in the enzalutamide arm and 31.3 mo (95% CI 28.8–34.2) in the placebo arm [18].

These findings led to regulatory approval for mCRPC patients after docetaxel in 2012 (FDA) and 2013 (EMA), and later for chemo-naïve patients in 2014 [15,17]. The TERRAIN and STRIVE trials showed survival benefits for enzalutamide in comparison with bicalutamide in the non-mCRPC or asymptomatic/minimally symptomatic mCRPC setting [19–21].

3.1.3. *Novel therapeutic hormonal agents*

Resistance to second-generation ADT agent enzalutamide or abiraterone may be primary or acquired [22,23]. Certain AR splice variants (AR-Vs), in particular AR-V7, measured in circulating tumor cells (CTCs) have been implicated in resistance to enzalutamide and abiraterone in preclinical and clinical studies [24]. In the context of precision oncology, measures of AR biology, including AR-Vs, will help select men with mCRPC most likely to benefit from AR-targeted therapies or select patients who are appropriate for other systemic approaches, for example, taxane chemotherapy.

Novel second-generation ADT agents with higher selectivity for 17,20-lyase or higher affinity to the AR may show better efficacy.

Orteronel (TAK-700) is a nonsteroidal, reversible, selective 17,20-lyase inhibitor. In 2015, orteronel failed to extend OS in two phase III trials of men with chemo-naïve mCRPC and mCRPC patients after chemotherapy [25,26]. This agent is currently being tested in the hormone-sensitive metastatic setting (NCT01809691).

Seviteronel (VT-464) is a nonsteroidal 17,20-lyase inhibitor that has higher selectivity for the inhibition of 17,20-lyase over hydroxylase [27]. Thus, interference with corticosteroid production is reduced in comparison with the approved CYP17 inhibitor abiraterone. Seviteronel is currently evaluated in several clinical phase II trials.

Apalutamide (ARN-509) binds the AR with five-fold greater affinity than bicalutamide and greater efficacy in murine xenograft models [28]. It has lower central nervous system penetration with reduced effect on gamma-aminobutyric acid A inhibition, which is thought to increase the risk of seizures (<1%) during enzalutamide therapy. In a

phase 2 trial in high-risk non-mCRPC, 89% of patients had ≥50% PSA decline at 12 wk [29]. In men with mCRPC, 80% of abiraterone acetate and prednisone (AAP)-naïve patients and 43% of post-AAP patients remained on treatment with apalutamide for 6 mo or longer [30].

This drug is currently under clinical evaluation in several different trials including evaluation in phase III studies, for example, in non-mCRPC (SPARTAN trial; press release announced positive data) and metastatic castration-sensitive PC (TITAN trial). To this end, a recent meta-analysis has suggested that metastasis-free survival (MFS) may be a good surrogate for OS in PC [31], lending credence to the MFS endpoint selected in the SPARTAN trial.

Darolutamide (ODM-201) is an AR antagonist with higher affinity to the AR than enzalutamide or ARN-509. In phase I and II clinical trials (ARADES), darolutamide was shown to be effective in men with mCRPC with a favorable safety profile [32]. Currently, two clinical phase III trials of darolutamide in men with non-mCRPC (ARAMIS trial) and metastatic hormone-sensitive PC (ARASENS trial) are ongoing. Once again, the primary endpoint selected for the ARAMIS trial is MFS.

3.1.3.1. Bipolar androgen therapy. PC cells can adapt to chronic androgen deprivation by autoregulatory increases in AR activity through alteration of the AR including amplification, deregulation, mutation, and post-translational modification [33]. However, a low-testosterone environment and AR overexpression induce vulnerability of CRPC cells to supraphysiological levels of androgens that can inhibit growth and promote cell death through inhibition of DNA relicensing and induction of double-strand DNA breaks. Schweizer et al used testosterone injections and concurrent ADT (termed bipolar androgen therapy [BAT]) to obtain rapid cycling between extremes of high and low levels of testosterone [34,35]. In combination with etoposide chemotherapy, this approach showed promising results in men with mCRPC. Several trials are currently investigating this paradoxical phenomenon with second-generation AR-targeted drugs, chemotherapy agents, or immunotherapeutics. A phase II study (NCT02090114) of BAT in men with mCRPC and progression on enzalutamide recently met its primary endpoint, with 30% ($n = 9$) showing PSA decline and 36% ($n = 5$) with measurable disease ($n = 15$) objective radiological response. Patients ($n = 30$) received testosterone cypionate (400 mg intramuscularly) every 4 wk and continued ADT. Upon progression on BAT, patients were rechallenged with enzalutamide [36]. The phase III strategy (TRANSFORMER trial) will randomize abiraterone-refractory mCRPC patients to enzalutamide versus BAT and is powered to show an improvement in radiographic progression-free survival using BAT in this setting (NCT02286921).

3.2. Chemotherapy

3.2.1. Docetaxel

Docetaxel was the first life-prolonging drug in men with mCRPC, and therefore, it has been the standard therapy for mCRPC in combination with prednisone since 2004 [1]. The cytotoxic agent mitoxantrone in combination with prednisone had improved palliation earlier, but median OS was 3 mo less in the TAX327 study that compared docetaxel and prednisone with mitoxantrone with prednisone. The TAX327 study randomly assigned 1006 men with mCRPC to receive docetaxel 75 mg/m^2 given once every 3 wk, mitoxantrone 12 mg/m^2 every 3 wk, or docetaxel 30 mg/m^2 given every week for 5 of every 6 wk, all with prednisone 5 mg twice daily [1]. All the other agents evaluated in patients who progressed after ADT such as corticosteroids, estrogens, ketoconazole, or radionuclides and bisphosphonates for bone-targeted therapy had shown no evidence of survival benefit.

Several clinical trials have focused on the role of taxane chemotherapy in men with hormone-naïve PC [37]. Previously, the randomized phase 3 GETUG-AFU15 trial failed to show significant improvement in OS in patients with metastatic hormone-sensitive PC [4]. However, patient accrual stopped in December 2008 and more patients received salvage docetaxel in the control arm, as newer drugs for mCRPC were not available at this time. In 2015, the Eastern Cooperative Oncology Group (ECOG) reported findings from the CHAARTED trial [38]. To assess whether concomitant treatment with ADT plus docetaxel would result in longer OS, 790 men were randomized to receive either ADT plus docetaxel (at a dose of 75 mg/m^2 of body-surface area every 3 wk for six cycles) or ADT alone. Men receiving ADT plus docetaxel showed a significant survival improvement compared with men with ADT alone (57.6 vs 44.0 mo; HR for death in the combination group 0.61; 95% CI 0.47–0.80; $p < 0.001$). In addition, ADT plus docetaxel was associated with longer progression-free survival (20.2 mo in the combination group, as compared with 11.7 mo in the ADT-alone group; HR 0.61; 95% CI 0.51–0.72; $p < 0.001$). Similarly, data from the STAMPEDE trial showed that addition of docetaxel chemotherapy at the beginning of long-term ADT improved progression-free survival and OS [39]. Thus, concomitant administration of up-front docetaxel chemotherapy and ADT in men with metastatic hormone-sensitive PC, especially in those with a high tumor burden, is associated with a significant benefit on OS [40]. Since accrual of both trials combining ADT with abiraterone was completed before the findings from the CHAARTED trial were reported, little data on a head-to-head comparison with docetaxel plus ADT are available currently, although some guidance on this topic is beginning to emerge [41].

3.2.2. Cabazitaxel

Cabazitaxel, a second-generation semisynthetic tubulin-binding taxane, led to significantly improved OS compared with mitoxantrone (both in combination with prednisone/prednisolone) in men with mCRPC whose disease has progressed during or after docetaxel-based therapy in the TROPIC phase III trial (median survival 15.1 mo [95% CI 14.1–16.3] in the cabazitaxel group and 12.7 mo [11.6–13.7] in the mitoxantrone group; HR 0.70 [95% CI 0.59–0.83]; $p < 0.0001$) [42]. Subgroup analyses showed efficacy of cabazitaxel in men with mCRPC refractory or resistant to docetaxel. Cabazitaxel also retains its antitumor activity in

mCRPC progressing after treatment with docetaxel and abiraterone or enzalutamide [43]. In the first-line setting, cabazitaxel did not demonstrate a survival benefit over docetaxel in patients with chemotherapy-naïve mCRPC (FIRSTANA trial) [44]. Both the FIRSTANA trial and the PROSELICA trial showed noninferiority for an alternative dosing regimen (dose reduction from 25 to 20 mg/m^2) with fewer treatment-related toxicities [44,45]. The TAXYNERGY trial evaluated the clinical benefit from early taxane switch in patients who did not achieve a $\geq$ 30% PSA reduction after four cycles and the usefulness of CTCs as a biomarker [46].

3.3. Immunotherapy

Active immune escape strategies protect prostate tumors from detection and destruction by the immune system [47]. Escape mechanisms include immune-suppressive cells (regulatory T cells and myeloid-derived suppressor cells), soluble factors (interleukin [IL]-6, IL-10, vascular endothelial growth factor, and transforming growth factor beta), and signaling pathways (immune checkpoints) [48]. Immunotherapeutic approaches are designed to enhance or reactivate antitumor immunity.

3.3.1. Therapeutic vaccines

3.3.1.1. Sipuleucel-T. Sipuleucel-T is the first and to date only immunotherapeutic that has shown a survival benefit among men with asymptomatic or minimally symptomatic mCRPC. As a type of therapeutic cancer vaccine, sipuleucel-T consists of autologous peripheral-blood mononuclear cells that have been activated ex vivo with a recombinant fusion protein. This fusion protein (PA2024) comprises prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor, an activator of immune cells. Sipuleucel-T is given every 2 wk for a total of three infusions, which are personalized and generated for each patient. In 2010, the phase III IMPACT trial showed a 4.1-mo improvement in median survival (25.8 mo in the sipuleucel-T group vs 21.7 mo in the placebo group) in 512 patients randomly assigned in a 2:1 ratio (sipuleucel-T vs placebo) [49]. Based on these results, sipuleucel-T was approved for the treatment of CRPC by the EMA (2013) and the FDA (2010). In 2015, the marketing company requested a withdrawal of the marketing authorization in the European Union for commercial reasons.

3.3.1.2. PROSTVAC-VF. PROSTVAC-VF is a cancer vaccine composed of an engineered poxviral vaccine targeting PSA-expressing tumor cells given along with a triad of human T-cell costimulatory molecules (B7.1, ICAM-1, and LFA-3, designated TRICOM) [50]. This therapeutic vaccine is designed to generate a robust immune response against PC cells. In a clinical phase 2 trial in 125 men with mCRPC, PROSTVAC-VF was well tolerated and was associated with an improvement of median OS of 8.5 mo and a 44% reduction in the death rate [50]. These promising results from clinical phase 2 trial led to the larger phase III PROSPECT study in men with asymptomatic or minimally symptomatic mCRPC (NCT01322490). Unfortunately, it was recently announced that the PROSPECT study did not meet its primary endpoint, so the future of PROSTVAC-VF (at least as a monotherapy) remains in question.

3.3.2. Immune checkpoint inhibitors

Immune checkpoints are stimulatory or inhibitory molecules in the immune system. Several immune checkpoints prevent the ability of the immune system of the host to respond to cancer cells. The blockade of inhibitory checkpoint molecules activates the immune system to fight tumors and has become a new target for cancer immunotherapies.

Ipilimumab is a monoclonal antibody that targets CTLA-4, a protein receptor for downregulation of the immune system. This checkpoint inhibitor was approved for the treatment of melanoma in 2011. A recent phase III trial did not show significant survival improvement with ipilimumab versus placebo ($p = 0.053$) following bone-directed radiotherapy in patients with mCRPC that had progressed after docetaxel chemotherapy [51]. However, very long-term survivors in complete response have been reported, an event usually not seen with nonimmunotherapies [52]. Recently, a phase III trial of ipilimumab in asymptomatic or minimally symptomatic patients with chemotherapy-naive mCRPC without visceral metastases also did not show a survival benefit for ipilimumab in comparison with placebo [53], although a proportion of patients achieved PSA and/or radiographic responses.

Nivolumab is a human monoclonal antibody against the programmed death receptor (PD-1) blocking PD-L1 from binding PD-1 on activated T cells and thereby allowing the immune system to attack cancer cells. Although there were objective responses in patients with non–small-cell lung cancer, melanoma, or kidney cancer, no responses were observed in patients with PC [54]. However, in a recent small clinical trial combining nivolumab plus ipilimumab in AR-V7+ mCRPC patients, clinical benefit was observed in four of 15 patients, suggesting that this combination may have activity in a subset of lethal PCs [55].

Graff and colleagues [56] demonstrated antitumor efficacy of the humanized anti–PD-1 antibody pembrolizumab in combination with enzalutamide in men with mCRPC after progression on enzalutamide in a phase II trial. After a median follow-up of 18 wk, 11 of 20 men treated showed a partial response ($n = 4$) or stable disease ($n = 7$) [56]. Similarly, Hansen et al [57] reported an overall response rate of 13% ($n = 3$) for pembrolizumab as a single agent in a phase Ib trial including 23 mCRPC patients. Nine other patients (39%) had stable disease. These encouraging preliminary data have led to the conduct of the KEYNOTE-199 study (NCT02787005), whereby mCRPC patients with measurable soft-tissue disease ($N = 100$ PD-L1+; $N = 100$ PD-L1–) and those with bone-only metastases ($N = 50$) will receive open-label pembrolizumab in an effort to better clarify the role of this agent in mCRPC.

In addition to PD-1 inhibitors, PD-L1 inhibitors are also being investigated. Currently, a phase III trial is comparing atezolizumab, a humanized antibody targeting PD-L1, with enzalutamide versus enzalutamide alone in patients with

mCRPC (IMbassador250, NCT03016312). Another human monoclonal antibody against PD-L1, avelumab, showed an acceptable safety profile in clinical phase 1 [58].

A unique application of PD-1 inhibitors, particularly pembrolizumab, is for the treatment of mCRPC patients with DNA mismatch repair (MMR) deficiency and/or microsatellite instability (MSI-high), following the FDA approval of pembrolizumab for cancers of any histology with MMR deficiency [59]. Although there are no dedicated clinical trials testing PD-1 inhibitors in PC patients with MMR deficiency, several anecdotal responses to pembrolizumab in MMR-deficient mCRPC have appeared in the literature [56,60]. Unfortunately, MMR deficiency is present in only about 2% of mCRPC patients, although this may be enriched in those with primary Gleason pattern 5 disease [61].

3.4. Bone-targeted therapy

The tropism of PC to bone explains high rates of up to 90% of bone metastases in men with mCRPC [62]. Management of bone metastases is important to prevent skeletal-related events (SREs) including pathological fractures (both symptomatic and found incidentally), spinal cord compression, and the requirement for surgery or radiation to bone for unstable or painful metastatic lesions. To maintain bone integrity during remodeling, homeostasis in the action of osteoblasts increasing bone mass and osteoclasts resorbing bone is required.

Bisphosphonates are rapidly absorbed onto the bone surface and inhibit osteoclast activity by affecting osteoclastogenesis, cell survival, and cytoskeletal dynamics. In 2002, a phase III trial showed that zoledronic acid, a third-generation bisphosphonate, significantly decreased the risk of SREs in men with mCRPC (44.2% vs 33.2% [placebo]; difference = –11.0%, 95% CI –20.3% to –1.8%; $p = 0.021$) [63].

The receptor activator of nuclear factor κB ligand (RANKL), a cytokine that binds to the RANK expressed by osteoclasts, is a key signaling molecule in the maintenance of bone integrity. Denosumab is a fully human monoclonal antibody directed against RANKL, which was randomly shown to be superior to zoledronic acid in prevention of SREs as well as delaying the time to first SRE (median time to first on-study SRE 20.7 mo [95% CI 18.8–24.9] with denosumab compared with 17.1 mo [15.0–19.4] with zoledronic acid; HR 0.82, 95% CI 0.71–0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority) [64]. A post hoc analysis of the COU-302 randomized trial suggested that concomitant bone-targeted agent (mostly denosumab and zoledronic acid) significantly improved OS (HR 0.75; $p = 0.01$) and increased the time to ECOG deterioration (HR 0.75; $p < 0.001$) and time to opiate use for cancer-related pain (HR 0.80; $p = 0.036$) compared with no bone-targeted agent use, suggesting that the benefit of abiraterone plus prednisone over prednisone alone may be increased by concomitant use of a bone-targeted agent [65]. In another phase 3 trial, denosumab had a statistically significant, but clinically nonmeaningful, impact for postponing the onset of bone metastases in men with non-mCRPC [66].

Radionuclides (eg, strontium-89 or samarium-152) can selectively bind to areas with enhanced bone turnover caused by metastases [33]. The alpha particle-emitting radium-223 mimics calcium and has a higher biological efficacy in causing tumor cell damage (dsDNA breaks) with more localized effect due to the very short range of alpha radiation, and less penetration of the surrounding tissue and subsequently less bone marrow damage [67]. In 2013, the ALSYMPCA trial showed improved survival for patients with mCRPC treated with radium-223 compared with placebo at the prespecified interim analysis (median OS 14.0 vs 11.2 mo; HR 0.70; 95% CI 0.55–0.88; two-sided $p = 0.002$). These results led to the approval for men with mCRPC and without known visceral metastases. Expanded access studies using this agent have demonstrated the safety and potential efficacy of using radium-223 concurrently with novel AR-directed therapies (abiraterone and enzalutamide) as well as denosumab [68].

3.5. Other emerging genetically targeted therapies and novel therapeutic targets

3.5.1. PARP inhibitors

The inhibition of poly(adenosine diphosphate–ribose) polymerase (PARP) in mCRPC tumors with DNA repair defects induces synthetic lethality [69]. The PARP inhibitor olaparib (AZD-2281) led to high response rates in patients who no longer responded to standard treatments for mCRPC and had defects in DNA repair genes [70]. In this study, 88% of all patients with homozygous deletions, deleterious mutations, or both in DNA repair genes including *BRCA1/2*, *ATM*, *Fanconi's anemia genes*, and *CHEK2* (16 of 49 patients) had a response to olaparib. The drug received FDA and EMA approval for germline BRCA mutated advanced ovarian and breast cancer that has received three or more prior lines of chemotherapy. Identification of defects in DNA damage repair genes by next-generation sequencing in mCRPC tumors may predict the antitumor activity of olaparib. Olaparib is currently being studied in the PROFOUND study (NCT02987543) in which men with homologous recombination-deficient PC (particularly those with *BRCA1/2* and *ATM* mutations) are being randomized to abiraterone/enzalutamide versus olaparib, using progression-free survival as the primary endpoint. Several other PARP inhibitors are currently under clinical evaluation including rucaparib (phase III trial TRITON3), niraparib, and talazoparib [71]. In addition, combination strategies, for example, with checkpoint inhibitors, are under clinical investigation.

Karzai et al [72] reported results from a phase II trial in men with mCRPC who received a combination therapy of olaparib and durvalumab hypothesizing that increased DNA damage induced by olaparib would complement the antitumor activity of durvalumab. Preliminary data showed this combination treatment to be well tolerated, with >50% PSA decline observed in five of seven patients after 2 mo.

The presence of germline DNA repair defects in men with mCRPC may be associated with a poor response to standard hormonal treatment, although the data are conflicting [73,74]. Pritchard et al reported a frequency of germline

DNA repair alterations in unselected men with advanced PC of about 12%, whereas only 4–5% of patients with localized PC and only 2–3% of patients without a cancer history harbor these mutations. This prevalence of germline mutations in recurrent/advanced PC (8–14%) has been confirmed by others [73–76]. Since tissue biopsies of metastatic lesions in mCRPC patients might not always be easy to obtain, detection of somatic DNA repair defects in circulating tumor DNA or germline mutations from a blood sample might facilitate selection of a patient subset that may be prioritized for PARP inhibition treatment [75,77].

3.5.2. Platinum-based chemotherapy

Platinum-based chemotherapy (cisplatin, carboplatin, and satraplatin) has shown antitumor activity in mCRPC, but these agents failed to improve survival in larger clinical trials. However, DNA repair defective mCRPC may benefit from chemotherapy with cisplatin or carboplatin. Given the possibility to identify DNA repair defects, platinum chemotherapy has been reevaluated. Tumor responses for carboplatin were reported in mCRPC patients with homologous recombination defects [78] and with biallelic BRCA2 loss [79]. Pomerantz et al [80] reported a higher likelihood of response to carboplatin-based chemotherapy for men with BRCA2-associated mCRPC (75%) than for men with non–BRCA2-associated mCRPC (17%) in a cohort of 141 men with mCRPC who received at least two doses of carboplatin.

3.5.3. Prostate-specific membrane antigen–targeted therapies

Prostate-specific membrane antigen (PSMA) is a receptor overexpressed on the surface of PC cells and tumor neovasculature. Small-molecule peptides with high binding affinity for the PSMA receptor allow high-quality positron emission tomography imaging. Labeling these PSMA peptides with radioisotopes, for example, lutetium 177 (^{177}Lu-PSMA-617) or actinium (^{25}Ac-PSMA-617), offers the option to administer radionuclide therapy to PSMA-positive mCRPC [81]. However, PSMA-expressing cells are also found in the small intestine, proximal tubules of the kidney, and salivary glands (with potential implications for off-target effects). In clinical trials, salivary and lacrimal glands have been identified to be most at risk when treated. Rathke et al reported their clinical observations of a cohort of 40 patients treated with ^{177}Lu-PSMA-617. Kratochwil et al [82,83] reported their experience with ^{25}Ac-PSMA-617 in men with mCRPC. A number of additional PSMA-directed radioligands are in development, as summarized in a recent review [84].

3.6. Treatment selection and optimal sequencing of agents in mCRPC

Within the past few years, several new agents were approved for the management of men with mCRPC. At the same time, little is known about optimal sequencing and combination strategies, and how cross resistance can evolve for subsequent treatments [85]. Predictive factors are missing to determine the optimal drug for patients eligible for multiple treatments. In an Italian retrospective analysis, clinical outcomes of third-line treatments in 260 patients were analyzed. All patients had received at least two agents (abiraterone, enzalutamide, or cabazitaxel) after docetaxel failure. No differences were observed in clinical outcomes of third-line treatments regardless of previous treatments [86].

Owing to paucity of available data on which patient responds best to which therapy [87,88], it becomes important to carefully monitor the course of disease and identify progress or resistance early. With several options available, alternative options have to be offered quickly. After failure of first-line treatment, currently several agents including novel hormonal therapy, cabazitaxel, and radium-223 are possible treatment options. Several guidelines and reviews recommend to select treatment options based on the existence of symptoms, prior treatments and clinical response, potential side effects and preexisting toxicity, patient's preference, comorbidities, life expectancy, quality of life, progression dynamics, tumor burden and localization of metastases (bone and visceral), and eligibility for chemotherapy (ECOG score, Karnofsky performance status, and a geriatric assessment [89]) [2,90]. For instance, novel hormonal therapies in general have better toxicity profiles compared with taxanes that have a higher incidence of adverse events. Consensus recommendations have been elaborated at the PC Saint Gallen meeting and are available [91].

Initial treatments may affect the potential benefit of subsequent treatments negatively. Therefore, sequential use of new agents in men with CRPC has to be optimized in order to obtain the best cumulative survival benefit. In a recent review, Handy and Antonarakis [87] published a suggested treatment algorithm for sequential therapy in mCRPC.

Cross resistance among therapeutics for mCRPC has been reported [92,93]. Clinical activity of abiraterone in mCRPC progressing after enzalutamide and conversely enzalutamide after abiraterone has been reported to be low [3]. Results from the CHAARTED and STAMPEDE trials, and the LATITUDE trial recently, showed high clinical activity of docetaxel and abiraterone in the metastatic castration-sensitive PC setting [12,13,38,39]. Recent data from GETUG-15 suggest that rechallenging docetaxel for CRPC progression in men who had previously received ADT plus docetaxel for metastatic castration-sensitive PC may have lower efficacy, while abiraterone or enzalutamide may retain activity in this setting [94]. Cabazitaxel seems to retain its antitumor activity in mCRPC progressing after docetaxel and resistant to abiraterone or enzalutamide [95]. Thus, further understanding of potential cross resistance is required. Alterations of the AR, for example, the AR-V7 that lacks the C-terminal ligand-binding domain but retains the transactivating N-terminal domain, were shown to be associated with resistance to AR-directed novel agents but not chemotherapeutic agents [96–98]. Al Nakouzi et al [95] showed that AR-V7 is a dynamic marker and that conversions from AR-V7 negative to positive occur in patients undergoing AR-directed therapies, whereas reversions from AR-V7 positive to negative seem to occur only with taxane chemotherapies.

Other alterations in AR signaling and increased androgen biosynthesis in the tumor microenvironment can lead to

resistance to hormonal therapy [3]. Induction of glucocorticoid receptor expression was found as an escape mechanism in enzalutamide-resistant tumors, leading to activation of similar target genes to the AR that are responsible for the resistant phenotype [99]. In addition, mCRPC patients with inherited or somatic homologous recombination deficiency might benefit from platinum-based treatment or PARP inhibitors, whereas MMR deficiency, MMR defects, and microsatellite instability might predict response to PD-1–based checkpoint inhibitors.

Therefore, further research and clinical trials of combination therapies with androgen biosynthesis inhibitors and AR antagonists may help overcome resistance and improve long-term outcomes.

4. Conclusions

Recent drug developments provide a range of five different therapeutic modalities for men with mCRPC in addition to docetaxel. All agents including the androgen synthesis inhibitor abiraterone, the AR inhibitor enzalutamide, the chemotherapeutic cabazitaxel, the immunotherapeutic sipuleucel-T, and the radionuclide radium-223 have shown significant impact on survival of these patients.

Despite this progress in development of new drugs, mCRPC continues to be incurable. Furthermore, the absence of durable complete responses requires chronic treatment. In the setting of noncurative therapy, all efforts therefore aim to prolong survival, palliate symptoms, improve and maintain quality of life, and prevent complications. Progression of disease experienced in most patients illustrates the need for novel therapeutic strategies. Recently developed drugs targeting the AR axis have shown that AR modulation remains a mainstay in the castration-resistant state. Future AR-directed therapeutic strategies may overcome resistance mechanisms, and may decrease intratumoral androgen biosynthesis and AR activity more effectively. Novel agents also target AR-independent oncogenic signaling pathways in mCRPC, with a renewed focus on the PARP pathway. With increasing therapeutic options, optimization of treatment selection and better understanding about sequencing strategies of current agents is urgently required. Identification of the right treatment in the right patient at the right time is the greatest challenge in mCRPC therapy. Prospective randomized clinical trials addressing the best therapy approaches in mCRPC are required to determine evidence-based sequencing strategies. Implementation of molecular and genetic findings, phenotypic characteristics, and identification of predictive biomarkers may help in the context of personalized mCRPC management to guide treatment decisions, improve clinical outcomes, and prevent unnecessary side effects and costly therapies in men with mCRPC.

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Study concept and design: All authors.
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Analysis and interpretation of data: All authors.
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