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Treatment of Advanced Prostate Cancer

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Abstract

The therapeutic landscape of prostate cancer has been transformed over the last decade by new therapeutics, advanced functional imaging, next-generation sequencing, and better use of existing therapies in early-stage disease. Until 2004, progression on androgen deprivation therapy for metastatic disease was treated with the addition of secondary hormonal manipulation; in the last decade, six systemic agents have been approved for the treatment of castration-resistant prostate cancer. We review clinical trials and survival benefit for these therapies and assess how the understanding of the disease shifted as these therapies were developed. We also discuss advances in non-castrate disease states, identification of biomarkers for prognosis and treatment selection, and opportunities in locoregional therapy to delay androgen deprivation therapy.

INTRODUCTION

Prostate cancer is among the most common cancer diagnoses in men, with more than 161,000 new cases diagnosed in the United States in 2017. While most cases run an indolent course without any threat to mortality, many patients present with intermediate or high-risk localized, locally advanced, or metastatic cancer and, despite treatment, succumb to the disease. As a result, prostate cancer is the third most common cause of cancer-related mortality among men in the United States (1).

Because prostate cancer has a long natural history, physicians have devised clinical states to conceptualize the disease, defined by primary tumor status, presence or absence of distant disease on imaging (metastatic versus nonmetastatic), testosterone levels (noncastrate versus castrate), and prior chemotherapy exposure (2, 3) (**Figure 1**). It has long been known that prostate cancer is unique in its dependence on androgen for growth and progression, and androgen deprivation is an effective therapeutic strategy that is widely used in clinical practice (4, 5). Disease progression despite castrate testosterone levels signals transition into a castration-resistant state. Once a patient enters a castration-resistant state, he is more likely to die of his prostate cancer than of other causes.

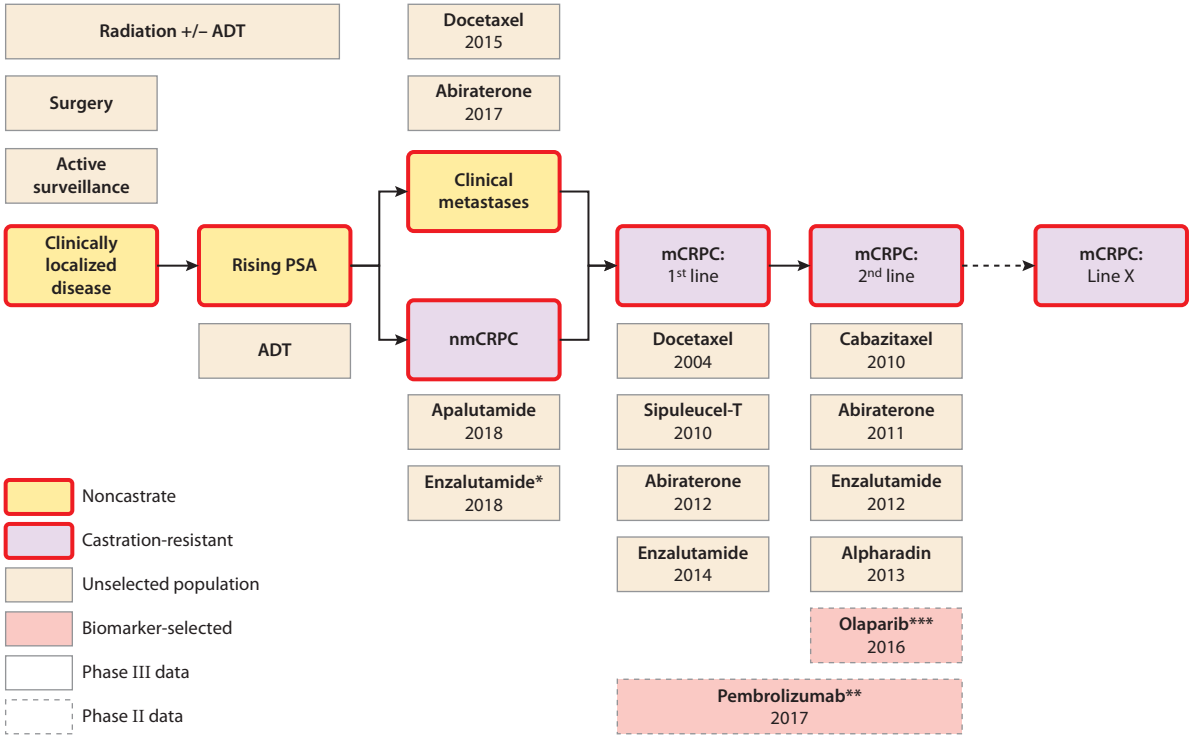

Figure 1

Model of prostate cancer clinical states proposed by Prostate Cancer Working Group 3 (3), with management options in different clinical states. Abbreviations: ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen. *Positive phase III data available but not approved by the US Food and Drug Administration (FDA). **Received FDA breakthrough designation based on phase II TOPARP-A trial. ***FDA approval based on tissue-agnostic microsatellite instability.

MANAGEMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Until 2004, progression on androgen deprivation therapy (ADT) for metastatic castration-resistant prostate cancer (mCRPC) was treated with the addition of secondary hormonal manipulation, including antiandrogens such as bicalutamide and nilutamide (6), ketoconazole (7), or corticosteroids (8). Mitoxantrone, the first cytotoxic chemotherapy approved for mCRPC by the US Food and Drug Administration (FDA), was approved on the basis of improved palliative responses in pain-related measures (9) despite no survival benefit (10).

Docetaxel, a microtubule inhibitor and the first systemic therapy to demonstrate survival benefit in mCRPC, was studied in two prospective phase III trials (11, 12). The TAX 327 trial randomized 1,006 patients to docetaxel plus prednisone every three weeks, weekly docetaxel, or mitoxantrone every three weeks. The Southwest Oncology Group (SWOG) 99–16 trial randomized 675 patients to docetaxel plus estramustine or mitoxantrone. In both studies, docetaxel administered every three weeks demonstrated clear survival benefit, with a median overall survival (OS) gain of 1.9 to 2.4 months, establishing docetaxel as the new standard of care for mCRPC in 2004. These trials also changed the understanding of CRPC and consequently influenced a generation of prospective clinical trials comparing chemotherapy-naive with postdocetaxel outcomes.

Tremendous progress in the systemic management of mCRPC has been made in the last decade, with six new agents approved in the United States specifically for the treatment of CRPC (13–20) and a seventh receiving breakthrough designation for accelerated development based on biomarker status (21).

ADT: androgen deprivation therapy

mCRPC: metastatic castration-resistant prostate cancer

OS: overall survival

PSA: prostate-specific antigen

SYSTEMIC THERAPY BEYOND DOCETAXEL

In addition to docetaxel, most agents for the treatment of mCRPC were approved based on demonstrable survival benefit in randomized studies. Therapies currently in clinical use are discussed in this section.

Cabazitaxel

Cabazitaxel is a tubulin-binding drug with demonstrated activity in docetaxel-resistant cancers. In the phase III TROPIC trial, patients who received cabazitaxel plus prednisone had longer progression-free survival (PFS) and OS compared to those who received mitoxantrone plus prednisone. However, 18 deaths were observed in the experimental arm compared to 9 in the mitoxantrone arm; 7 deaths in the experimental arm were caused by clinical consequences of neutropenia or sepsis (13). A follow-up phase III study, PROSELICA, found a lower dose of cabazitaxel, 20 mg/m^2, to be noninferior to the TROPIC dose, 25 mg/m^2 (22). In view of its clinical activity in the post-docetaxel setting, cabazitaxel was also studied in a three-arm phase III trial, FIRSTANA, which evaluated 20 mg/m^2 or 25 mg/m^2 doses against docetaxel as first-line chemotherapy in mCRPC. The trial showed no difference in median OS (24.5 versus 25.2 versus 24.3 months) but slightly different toxicity profiles: Febrile neutropenia, neutropenic infection, diarrhea, and hematuria were reported more frequently among patients receiving cabazitaxel, while peripheral neuropathy, stomatitis, peripheral edema, alopecia, and nail disorders were observed more frequently among those receiving docetaxel (23). The phase II TAXYNERGY trial examined the benefit of early switch from docetaxel to cabazitaxel, or vice versa, in mCRPC patients who did not achieve an optimal prostate-specific antigen (PSA) response, defined as >30% decline from baseline, by cycle 4. Almost 25% of patients did not achieve >30% PSA response and

therefore switched to the other taxane. Of those patients who switched, 46.7% achieved >50% PSA response. It is unknown if this approach confers survival benefit (24).

PFS: progression-free survival

Abiraterone Acetate

Abiraterone acetate is a selective inhibitor of cytochrome P (CYP) 17, a key enzyme in androgen synthesis. Early in the development of abiraterone acetate, research showed that inhibition of CYP17 could increase adrenocorticotropic hormone (ACTH) levels up to sixfold. Elevated ACTH can result in mineralocorticoid excess, which can be countered with corticosteroids (25). Compared to prednisone alone, the combination of abiraterone acetate and prednisone in both the pre- and post-docetaxel settings demonstrated superior gains (26, 27) in all clinical measures, including time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, decline in performance status, and OS. In the phase III COU-AA-301 trial, which enrolled 1,195 patients who had previously received docetaxel, those in the abiraterone arm had significantly longer median OS (14.8 versus 10.9 months), the primary endpoint, with a 35% decrease in risk of death. The study was unblinded at interim analysis because of the magnitude of the benefit over prednisone alone (26). The phase III COU-AA-302 trial, in contrast, enrolled 1,088 chemotherapy-naive patients with mCRPC and had coprimary endpoints of radiographic PFS and OS. The study was unblinded after an interim analysis, and patients in the abiraterone arm had significant improvement in median radiographic PFS (16.5 versus 8.3 months); however, the trial was criticized for premature unblinding, and therefore the OS result did not cross the efficacy boundary, despite the superior OS associated with abiraterone (27). With further follow-up, a survival advantage was demonstrated (28). Abiraterone acetate is well tolerated, with most side effects related to mineralocorticoid excess.

Enzalutamide

Enzalutamide is a targeted androgen receptor inhibitor, identified and optimized from a large-scale screening of more than 200 nonsteroidal antiandrogens that retain activity when androgen receptor expression is increased (29). It binds competitively to the ligand-binding domain of the androgen receptor and inhibits androgen receptor translocation to the cell nucleus and androgen receptor binding to DNA. Its clinical activities were established in two phase III trials—PREVAIL and AFFIRM. In the PREVAIL trial, 1,717 chemotherapy-naive patients with mCRPC were randomized to enzalutamide or placebo. The trial had co-primary endpoints of radiographic PFS and OS. At 12-month follow up, radiographic PFS was 65% in patients who received enzalutamide compared to 14% in the placebo arm. At the first interim analysis, median OS improved in the enzalutamide arm (32.4 versus 20.3 months), with a 29% decrease in risk of death, leading the Data and Safety Monitoring Committee to recommend unblinding and crossover (18). The AFFIRM trial randomized 1,199 men with prior docetaxel exposure 2:1 to enzalutamide or placebo. The primary endpoint was met: Patients who received enzalutamide had higher median OS (18.4 versus 13.6 months), with a 37% decrease in risk of death (17).

Radium-223

Radioisotopes such as samarium-153 (30, 31) and strontium-89 (32, 33) have long been a therapeutic option, either as monotherapy or in combination with chemotherapy, in the management of advanced prostate cancer. While no survival benefit had been shown, radioisotopes offer symptomatic palliation, especially in men with high-volume, osseous metastatic disease. Nevertheless,

these isotopes are beta emitters with potential to cause marrow toxicity. Radium-223 is an alpha-emitting calcium mimetic that binds to the microenvironment of sclerotic metastases with a considerably narrower range of irradiation compared with beta emitters and, therefore, lower risk of hematologic complications. While the PSA response rate is low (34), dose-dependent pain palliation is observed (35). The phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial randomized patients who had prior exposure to docetaxel or were ineligible for docetaxel 2:1 to radium-223 treatment or placebo and showed an OS gain (14.9 versus 11.3 months). Interestingly, toxicity rates were consistently lower in the radium-223 arm than in the placebo arm (15). The follow-up phase III ERA 223 study investigated radium-223 with or without the addition of abiraterone acetate. This study was unblinded and halted early, following an Independent Data Monitoring Committee recommendation, when higher rates of death or fracture were observed in the combination arm (36).

Sipuleucel-T

Sipuleucel-T is an autologous cellular immunotherapy approved for treatment of asymptomatic or minimally symptomatic mCRPC. It is composed of autologous antigen-presenting cells cultured with a fusion protein, PA2024, which consists of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (37). Three phase III trials—D9901, D9902A, and D9902B—confirmed its efficacy, along with a companion crossover phase II study, APC8015F (38). In D9901, 127 patients were randomized 2:1 to receive three infusions of sipuleucel-T or placebo every two weeks for up to three doses. No differences in the primary endpoint, time to progression, were noted, but the experimental arm had superior OS (25.9 versus 21.4 months) (37). D9902A had a similar design and the same endpoint as D9901; however, enrollment was halted after 98 patients, given the initial primary endpoint analysis from D9901. An integrated analysis of both studies (D9901 and D9902A) confirmed the median OS gain (23.2 versus 18.9 months), with a 33% decrease in risk of death. A trend toward improved PFS was noted but did not reach statistical significance (39). On the basis of these observations, D9902B [the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial] was amended into an independent phase III study with OS as the primary endpoint. With 512 patients enrolled, the study confirmed the survival benefit of 4.1 months (median OS 25.8 versus 21.7 months). Time to progression was similar in both arms (14). A follow-up crossover analysis moved 66.3% of patients in the control arm to APC8015F, with cells cryopreserved at the time of control production reinfused following disease progression. After adjusting for potential prognostic variables, the estimated median OS secondary to crossover in the control arm ranged from 3.9 to 8.1 months, suggesting that the survival benefit of sipuleucel-T might be more robust than previously thought (38).

Olaparib

Poly(ADP–ribose) polymerase (PARP) inhibition has long been explored as a therapeutic strategy for breast and ovarian cancers, especially in cases with underlying *BRCA1/2* or other germline DNA damage repair defects. Large-scale multicenter efforts recently demonstrated germline defects in DNA damage repair genes in up to 11.8% of men with advanced prostate cancer (40). A comparable proportion of mCRPC will harbor somatic alterations in these genes as well (41), suggesting the potential benefit of PARP inhibition in prostate cancer. Further confirming this hypothesis, the phase II TOPARP-A trial showed a 33% response rate to olaparib in 50 patients with heavily pretreated mCRPC. Fourteen of the 16 patients with homologous deletions or deleterious mutations in DNA damage repair genes responded to olaparib. Overall, biomarker-positive

patients experienced superior median PFS (9.8 versus 2.7 months) and median OS (13.8 versus 7.5 months) (21). Given these findings, the FDA granted breakthrough designation for olaparib in mCRPC to accelerate its development and review.

Pembrolizumab

Immune checkpoint inhibitors, despite their practice-changing clinical outcomes in other solid tumors, have yet to demonstrate efficacy in prostate cancer. Ipilimumab, an anticytotoxic T-lymphocyte-associated 4 (CTLA4) checkpoint inhibitor, was investigated in two phase III trials in mCRPC, both of which failed to achieve their primary endpoint, OS (42, 43). Nevertheless, the drug showed some clinical activity, such as improved PFS and PSA responses. With anti–programmed cell death protein 1/programmed death ligand 1 (PD1/PDL1) checkpoint inhibitors, initial multi-disease phase I studies indicated low activity in CRPC; there were no responses in 17 cases of mCRPC with nivolumab (44) and 3 with pembrolizumab (45). In a single-center phase II study (46), 3 of 10 patients who progressed on enzalutamide experienced biochemical response, 2 of whom achieved a radiographic partial response. However, the response rate was not replicated in the larger Keynote-199. Three study arms have been reported to date: (*a*) patients with RECIST-measurable PD-L1+ disease ($n = 131$), (*b*) RECIST-measurable PD-L1– disease ($n = 67$), and (*c*) patients with nonmeasurable, bone-predominant disease ($n = 60$). All patients were heavily pretreated with androgen signaling-targeting agent and cytotoxic chemotherapy. The primary endpoint of overall response rate (RECIST v 1.1 by central review) was achieved in 5% of patients within the first two groups (47). Across all three cohorts, disease control rate (CR + PR + SD) lasting ≥6 months was 11%. Furthermore, PSA decline of >50% was observed only in 11% of the entire study cohort to date. More recently, pembrolizumab showed a high response rate in tumors with mismatch repair deficiency, regardless of primary site (48), leading to a tissue-agnostic FDA approval. With some studies suggesting that 2–12% of prostate cancers harbor microsatellite instability and a hypermutated state (49, 50), pembrolizumab represents a new therapeutic option for a subset of mCRPC. However, notably, only one patient with prostate cancer was enrolled in the pembrolizumab study, and therefore the true activity of anti-PD1 checkpoint inhibition, even in a biomarker-selected mCRPC setting, is yet to be fully evaluated. Recently, it was shown that up to 5% of mCRPC might harbor functionally significant alterations in *CDK12* and that these tumors were associated with a higher neoantigen burden, which might increase the likelihood of response to immune checkpoint inhibition, although this remains to be demonstrated in a clinical setting (51).

SHIFTING NOMENCLATURE AND CLASSIFICATION OF PROSTATE CANCER

Recognizing the large number of therapies developed and approved over the last decade and the limitations of the chemo-naive versus post-docetaxel dichotomy, the latest iteration of the Prostate Cancer Working Group (PCWG3), first convened to develop consensus for clinical trial endpoints in prostate cancer, recommended replacing the pre- versus post-chemotherapy distinction with a dynamic classification. This new classification considers the lines of therapy a patient has received independent of the mechanism of action of each one, the order in which they were administered, and the sensitivity of the tumor to each (3). It also emphasizes the importance of sequencing systemic therapy in mCRPC, as many questions remain regarding optimal sequencing of treatments and response. Reassuringly, preliminary studies have already been undertaken, including a recent study showing that both abiraterone and enzalutamide conferred comparable activity in the first-line mCRPC setting (52), as well as the TAXYNERGY trial discussed above (24).

For men with localized prostate cancer, definitive therapy—either radical prostatectomy or radiotherapy—is curative in most instances. Nevertheless, a subset of patients, characterized by features such as high Gleason score, higher PSA at diagnosis, and greater disease burden in the primary tumor, are at heightened risk of relapse, with biochemical recurrence rate exceeding 50% at five years (53). In a large single-center series, PSA doubling time and Gleason score were independent predictors for development of metastatic disease in patients with biochemical recurrence (54, 55). While conventional ADT remains the standard of care for patients with a biochemical recurrence and rapidly rising PSA, castration resistance eventually emerges (56). In fact, a large analysis showed that the likelihood of bone metastasis or cancer-related death increases when the PSA doubling time decreases to less than eight months (57).

nmCRPC: "nonmetastatic" castration-resistant prostate cancer

MFS: metastasis-free survival

Recently, investigators have focused on treatment for men with "nonmetastatic" CRPC (nmCRPC). This disease state is defined by the presence of biochemical progression despite castrate levels of testosterone and no evidence of metastases on conventional scans. It is assumed that with more sensitive imaging techniques, many of these patients would show metastases. With that said, two large phase III studies with similar design and rationale, SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) and PROSPER, demonstrated that next-generation androgen receptor inhibitors with comparable mechanisms of action (apalutamide and enzalutamide, respectively) significantly delayed the time to development of radiographic disease (**Table 1**).

The SPARTAN trial enrolled 1,207 CRPC patients at high risk of metastatic disease, defined by PSA doubling time of 10 months or less at biochemical progression during ADT. Over 70% of patients had PSA doubling times of 6 months or less. Patients were randomized to receive apalutamide or placebo with concurrent ADT, with a primary endpoint of metastasis-free survival (MFS). The use of apalutamide in nmCRPC significantly increased median MFS (40.5 versus 16.2 months) (16).

The PROSPER trial, where 1,401 patients received enzalutamide or placebo upon biochemical progression on ADT, mirrored the observations from SPARTAN. Similarly, most patients had a PSA doubling time of 6 months or less. In this trial, enzalutamide significantly delayed the time to development of metastasis on conventional imaging compared to placebo (median MFS 36.6 versus 14.7 months) (58).

Despite these strongly positive results for MFS as the primary endpoint for nmCRPC, survival benefit has not yet been clearly shown. A large analysis called ICECaP (Intermediate Clinical Endpoints in Cancer of the Prostate) showed that MFS is a strong surrogate for OS in localized prostate cancer (59), but this result has not been applied to CRPC. Based on the MFS data alone, apalutamide was approved in 2018 for the treatment of nmCRPC.

NONCASTRATE PROSTATE CANCER—THE NEW FRONTIER

Despite advances in the therapeutic landscape, most mCRPC patients will eventually experience disease progression and succumb to prostate cancer. Noncastrate disease states, shown to harbor lower genetic heterogeneity and complexity (41), have attracted interest because of the potential opportunity to use existing therapies to improve clinical outcomes.

Contemporary Imaging Techniques

Determination of clinical state, especially to distinguish between metastatic and nonmetastatic disease and plan a treatment strategy, depends largely on available imaging modalities. Conventional imaging modalities are limited by their low sensitivity. Furthermore, bone scintigraphy, including

Table 1 Completed phase III clinical trials with an overall survival benefit in advanced prostate cancer

Clinical state	Study	*n*	Cohorts	Clinical measure	Disease-free survival (months)				Overall survival (months)			
					Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value	Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value
nmCRPC	SPARTAN (16) Apalutamide + ADT versus placebo + ADT	1,207	NA	Met.-free survival	40.5	16.2	0.28 (0.23–0.35)	<0.001	ND	39	0.70 (0.47–1.04)	0.07
	PROSPER (58) Enzalutamide + ADT versus placebo + ADT	1,401	NA	Met.-free survival	36.6	14.7	0.29 (0.24–0.35)	<0.001	ND	ND	0.80 (0.58–1.09)	0.1519
mHSPC	LATITUDE (20) ADT + abiraterone + prednisone versus ADT + placebo + placebo	1,199	NA	Radiographic progression-free survival	33.0	14.8	0.47 (0.39–0.55)	<0.001	66% at 3 years	49% at 3 years	0.62 (0.51–0.76)	<0.001
	STAMPEDE (19) ADT + abiraterone + prednisone versus ADT	1,917	NA	Failure-free survival	75% at 3 years	45% at 3 years	0.29 (0.25–0.34)	<0.001	83% at 3 years	76% at 3 years	0.63 (0.52–0.76)	<0.001

(*Continued*)

Table 1 (*Continued*)

Clinical state	Study	*n*	Cohorts	Clinical measure	Disease-free survival (months)				Overall survival (months)			
					Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value	Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value
mHSPC (*continued*)	CHAARTED (62, 63) ADT + docetaxel versus ADT	790	Entire cohort	Time to clinical progression	33.0	19.8	0.61 (0.50–0.75)	<0.001	57.6	47.2	0.72 (0.59–0.89)	0.0018
			High-volume disease	Time to clinical progression	27.3	13.0	0.53 (0.42–0.67)	<0.001	51.2	34.4	0.63 (0.50–0.79)	<0.001
			Low-volume disease	Time to clinical progression	42.5	44.3	0.86 (0.60–1.25)	0.43	63.5	ND	1.04 (0.70–1.55)	0.86
	STAMPEDE (64) ADT + docetaxel versus ADT + docetaxel + zoledronic acid versus ADT[a]	2,962	Entire cohort, docetaxel + ADT versus ADT	Failure-free survival	37	20	0.61 (0.53–0.70)	<0.001	81	71	0.78 (0.66–0.93)	0.006
			Entire cohort, docetaxel + zoledronic acid + ADT versus ADT	Failure-free survival	36	20	0.62 (0.54–0.70)	<0.001	76	71	0.82 (0.69–0.97)	0.022
			Met. cohort, docetaxel + ADT versus ADT	Failure-free survival	ND	ND	0.61 (0.53–0.71)	<0.001	60	46	0.76 (0.62–0.92)	0.005
			Met. cohort, docetaxel + zoledronic acid + ADT versus ADT	Failure-free survival	ND	ND	ND	ND	55	46	0.79 (0.66–0.96)	0.015

(*Continued*)

Table 1 (*Continued*)

Clinical state	Study	*n*	Cohorts	Clinical measure	Disease-free survival (months)				Overall survival (months)			
					Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value	Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value
Chemo-naïve mCRPC	IMPACT (14) Sipuleucel- T versus placebo	512	NA	Time to progression	3.7	3.6	0.95 (0.77–1.17)	0.63	25.8	21.7	0.78 (0.61–0.98)	0.03
	COU-AA-302 (27) Abiraterone + prednisone versus placebo + prednisone	1,088	NA	Radiographic progression-free survival	ND	8.3	0.43 (0.35–0.52)	<0.001	ND	27.2	0.75 (0.61–0.93)	0.01
	PREVAIL (18) Enzalutamide versus placebo	1,717	NA	Time to PSA progression	11.2	2.8	0.17 (0.15–0.20)	<0.001	32.4	30.2	0.71 (0.60–0.84)	<0.001
Chemo in chemo-naive mCRPC	TAX 327 (12) Docetaxel + prednisone versus mitoxantrone + prednisone	1,006	Docetaxel 3× weekly	ND	ND	ND	ND	ND	18.9	16.5	0.76 (0.62–0.94)	0.009
			Docetaxel weekly	ND	ND	ND	ND	ND	17.4	ND	0.91 (0.75–1.11)	0.36
	SWOG 99–16 (11) Docetaxel + estramustine versus mitoxantrone + prednisone	770	NA	ND	ND	ND	ND	ND	17.5	15.6	0.80 (0.67–0.97)	0.02

(*Continued*)

Table 1 (*Continued*)

Clinical state	Study	*n*	Cohorts	Clinical measure	Disease-free survival (months)				Overall survival (months)			
					Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value	Exp. arm	Con. arm	Hazard ratio (95% CI)	*p* Value
Post-docetaxel mCRPC	COU-AA-301 (26) Abiraterone + prednisone versus placebo + prednisone	1,195	NA	Time to PSA progression	10.2	6.6	0.58 (0.46–0.73)	<0.001	14.8	10.9	0.65 (0.54–0.77)	<0.001
				Radiographic progression-free survival	5.6	3.6	0.67 (0.58–0.78)	<0.001				
	AFFIRM (17) Enzalutamide versus placebo	1,199	NA	Time to PSA progression	8.3	3.0	0.25 (0.20–0.30)	<0.001	18.4	13.6	0.63 (0.53–0.75)	<0.001
				Radiographic progression-free survival	8.3	2.9	0.40 (0.35–0.47)	<0.001				
	ALSYMPCA (15) Alpharadin versus placebo	921	NA	Time to PSA progression	3.6	3.4	0.64 (0.54–0.77)	<0.001	14.9	11.3	0.70 (0.58–0.83)	<0.001
	TROPIC (13) Cabazitaxel + prednisone versus mitoxantrone + prednisone	755	NA	Progression-free survival	2.8	1.4	0.74 (0.64–0.86)	<0.001	15.1	12.7	0.70 (0.59–0.83)	<0.001

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; Con., control; Exp., experimental; mCRPC, metastatic castration-resistant prostate cancer; Met., metastasis; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; ND, not described; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific androgen.
[a]ADT + zoledronic acid arm not included in the table.

^{99m}Tc-based and ^{18}F-NaF positron emission tomography (PET) imaging, records osteoblastic activity and, therefore, does not reflect true disease volume or activity. As alluded to above, the increasing availability of modern functional imaging modalities, especially with recent FDA approval of ^{11}C-choline (60) and ^{18}F-fluciclovine (61) PET and the rising use of PET imaging based on prostate-specific membrane antigen, is improving detection of occult metastatic disease not visualized with more conventional imaging modalities in patients with high-risk localized cancer and with biochemical recurrence, effectively increasing the pool of patients with metastatic noncastrate prostate cancer.

mHSPC: metastatic hormone-sensitive prostate cancer

FFS: failure-free survival

Metastatic Hormone-Sensitive Prostate Cancer

Both docetaxel and abiraterone acetate have demonstrated meaningful clinical activity in metastatic hormone-sensitive prostate cancer (mHSPC) (see **Table 1**). The phase III E3805/CHAARTED trial (ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) randomized patients with mHSPC to six cycles of docetaxel plus ADT or ADT alone. Intended to enroll only patients with high disease burden, defined by the presence of visceral metastases (a bone metastasis burden beyond the axial skeleton) or by high number of lesions, the trial was later amended to enroll patients with low disease burden as well (62). Overall, the addition of docetaxel conferred a median OS advantage of 13.6 months over ADT alone. This benefit was most apparent and significant among patients with high disease burden and was maintained in these patients at 54-month follow up. However, patients with low disease burden had no survival benefit after docetaxel addition (63). Similar survival outcomes were seen with the docetaxel and docetaxel plus zoledronic acid arms in the large multicenter multi-arm MRC STAMPEDE (Medical Research Council Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial, which enrolled patients with metastatic, nodal, or high-risk localized disease. While subgroup analysis showed clinical benefit most pronounced and significant in metastatic disease, the study was not designed and did not have the power to evaluate clinical benefit in each clinical subgroup (64). Interestingly, chemotherapy for mHSPC was also examined by the GETUG (Groupe d'Étude des Tumeurs Urogénitales)–15 trial, which failed to demonstrate a survival advantage (65). Longer-term follow up, along with restratification of mHSPC by disease burden per CHAARTED, suggested a trend in favor of docetaxel in the subgroup with high disease volume (66). More recently, the abiraterone arm of the MRC STAMPEDE trial was reported. Inclusion criteria were similar to those for the docetaxel arms. Almost 50% of patients had metastatic disease, and ~20% had nodal disease. The trial demonstrated significant OS benefit: 83% three-year survival with abiraterone compared to 76% with ADT alone. Improvement in failure-free survival (FFS) occurred across all subgroups (19). The survival advantage among metastatic patients was replicated in the contemporaneous LATITUDE trial, which enrolled only patients with high-risk metastatic disease, defined by at least two of the following: Gleason score of 8 or higher, three or more bone metastases, three or more visceral metastases. In the study, OS rates at three years were 66% for the abiraterone plus ADT arm and 49% for the ADT arm, translating to a 38% reduction in risk of death with the addition of abiraterone (20).

A recent analysis of the abiraterone acetate and docetaxel arms of the MRC STAMPEDE trial compared patients enrolled during the same period. The observed PFS, FFS, and MFS data appear to favor abiraterone, in part because of its continuous administration. However, cancer-specific survival and OS were identical, reinforcing that each agent is a reasonable approach to the treatment of mHSPC (67).

BIOMARKERS FOR PROGNOSIS AND TREATMENT SELECTION

Biomarkers, characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (68), can be disease- or host-related. Many biomarkers have been proposed for prognostication or direct therapy, but few have been rigorously verified or validated. With advances in next-generation sequencing and its falling costs, much has been learned about the genomic basis of advanced prostate cancer and its response to therapy. In fact, many ongoing studies are developed based on our genomic understanding of the disease (**Table 2**).

Prostate cancer is androgen dependent, and therefore the androgen receptor (AR) is one of the most important oncogenic drivers of disease. Androgen receptor splice variant 7 (AR-V7) confers resistance to both enzalutamide and abiraterone in mCRPC because it is constitutively active despite lacking a ligand-binding domain (69). Conversely, the presence of AR-V7 does not appear to impair taxane response (70). In addition to this mechanism, AR amplification or point mutation can also confer resistance to next-generation anti-AR-targeted therapies (71).

The proportion of men with advanced prostate cancer who harbor germline alterations in DNA damage repair genes, such as *BRCA1*, *BRCA2*, *ATM*, or *CHEK2* (40), is ~12%—considerably higher than among men with localized disease or in the general population. However, clinical data on the impact of DNA damage repair gene alterations on disease biology and treatment response are conflicting. While somatic alterations in these genes might be associated with better prognosis among men treated with abiraterone and veliparib (72), in some studies germline DNA repair defects have been shown to exhibit poor responses to standard hormonal therapies (73). These seemingly contradictory findings require further investigation. Most importantly, DNA repair defects might portend superior response to PARP inhibition (21).

Additional biomarkers are at different stages of development and evaluation. To date, the biomarker showing the largest potential clinical implications is microsatellite instability status (41, 49, 74), especially supported by the recent tissue-agnostic approval of pembrolizumab across cancer types (see discussion above).

LOCOREGIONAL THERAPY IN METASTATIC PROSTATE CANCER

By convention, systemic therapy remains the primary treatment modality for metastatic disease. There is increasing interest in the role of locoregional therapies in this disease state in recent times.

Radical Prostatectomy in Metastatic Disease

For men with high-risk localized disease, radical prostatectomy with pelvic lymph node dissection reduces the risk of cancer-related death (75). For men with metastatic prostate cancer, radical prostatectomy has been shown to be feasible and safe (76, 77), although the survival benefit is less certain because it has not been formally confirmed in a prospective, randomized setting (78–80). Nevertheless, large retrospective series analyses and population-based data suggest a survival benefit. In an analysis of the SEER (Surveillance, Epidemiology, and End Results) database of more than 8,000 men with metastatic prostate cancer, the five-year OS and disease-specific survival rates were higher for patients who underwent radical prostatectomy (67.4% and 75.8%) than for those who underwent brachytherapy (52.6% and 61.3%) or those without local therapy (22.5% and 48.7%) (79), and the benefit persisted even after accounting for heterogeneity with propensity analysis (78).

Table 2 Selected ongoing phase III trials in advanced prostate cancer (data from ClinicalTrials.gov accessed April 25, 2018)

Pathway/ mechanism	NCT number	Title	Acronym	Recruitment	Interventions	Start date
Androgen receptor axis	NCT01949337	Enzalutamide With or Without Abiraterone and Prednisone in Treating Patients With Castration-Resistant Metastatic Prostate Cancer	None	Active, not recruiting	Drug: enzalutamide Drug: abiraterone Drug: prednisone	1/1/14
	NCT01957436	A Phase III of ADT + Docetaxel +/− Local RT +/− Abiraterone Acetate in Metastatic Hormone-naive Prostate Cancer	PEACE1	Recruiting	Drug: abiraterone acetate Radiation: radiotherapy Other: androgen deprivation therapy Drug: docetaxel	11/13/13
	NCT02257736	An Efficacy and Safety Study of Apalutamide (JNJ-56021927) in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Participants With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)	None	Active, not recruiting	Drug: apalutamide Drug: abiraterone acetate Drug: prednisone Drug: placebo	11/26/14
	NCT02489318	A Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC	TITAN	Active, not recruiting	Drug: apalutamide Drug: placebo Drug: androgen deprivation therapy	11/27/15
	NCT02677896	A Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)	ARCHES	Active, not recruiting	Drug: enzalutamide Drug: placebo	3/7/16
	NCT02799602	ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer	ARASENS	Recruiting	Drug: BAY1841788/Darolutamide (ODM-201) Drug: standard androgen deprivation therapy Drug: docetaxel Drug: placebo	11/30/16

(*Continued*)

Table 2 (*Continued*)

Pathway/ mechanism	NCT number	Title	Acronym	Recruitment	Interventions	Start date
DNA damage repair	NCT02975934	A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	TRITON3	Recruiting	Drug: rucaparib Drug: abiraterone acetate or enzalutamide or docetaxel	1/1/2017
	NCT02987543	Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer	PROfound Study	Recruiting	Drug: olaparib Drug: enzalutamide Drug: abiraterone acetate	2/6/2017
	NCT03395197	Talazoparib + Enzalutamide versus Enzalutamide Monotherapy in DDR + mCRPC	TALAPRO-2	Recruiting	Drug: talazoparib with novel hormone therapy Drug: placebo with novel hormone therapy	12/18/17
Immune checkpoint	NCT03016312	A Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) After Failure of an Androgen Synthesis Inhibitor And Failure of, Ineligibility For, or Refusal of a Taxane Regimen	IMbassador250	Recruiting	Drug: atezolizumab Drug: enzalutamide	1/11/2017
PI3K/AKT	NCT03072238	Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients With Metastatic Castrate-Resistant Prostate Cancer	IPATential150	Recruiting	Drug: ipatasertib Drug: abiraterone Drug: placebo	6/30/17
Radioisotope	NCT03458559	Rhenium-188-HEDP versus Radium-223-chloride in Patients With Advanced Prostate Cancer Refractory to Hormonal Therapy	RaRe	Not yet recruiting	Drug: radium-223 chloride Drug: rhenium-188-HEDP	4/1/2018
	NCT02194842	Phase III Radium 223 mCRPC-PEACE III	PEACE III	Recruiting	Drug: radium-223 Drug: enzalutamide	10/1/2015

Abbreviations: DDR, DNA damage repair; PD-L1, programmed death ligand 1; PI3K, phosphatidylinositol 3-kinase.

Stereotactic Body Radiotherapy

Although there is no consensus definition for oligometastatic osseous disease, several bony lesions are strongly correlated with survival in mCRPC (81, 82). Interest in targeted management of low-volume metastatic disease has increased with single-center studies reporting ADT-free intervals of 25 to 40 months (83, 84) and short-term local PFS rates of 79% to 99% (85). Most of these studies used up to three sites of bony metastases as an acceptable threshold for stereotactic body radiotherapy. More recently, this approach was reported in a multicenter prospective phase II trial. Patients with oligometastatic disease were randomized to observation or metastasis-directed therapy, including surgery and radiotherapy. With ADT slated to commence at symptomatic progression, at progression to more than three metastatic lesions, or at local progression of known metastasis, locoregional therapies increased the ADT-free interval (86). The true value of this approach with respect to survival or improved quality of life has yet to be demonstrated.

Multimodality Strategy for Advanced Prostate Cancer—Is the Future Here Yet?

Recent results have encouraged exploration of a multimodal strategy in oligometastatic advanced prostate cancer, especially because studies suggest that each modality contributes to further disease debulking and, thus, disease control (87). Several studies are evaluating this strategy, including PEACE1 (NCT01957436), MetaCure (NCT03436654), and the radiotherapy arm of MRC STAMPEDE.

CONCLUSION

The therapeutic landscape of prostate cancer has considerably broadened over the last decade. Advanced prostate cancer is not limited to mCRPC but includes mHSPC and even some localized disease characterized by high-risk features. These advances coincide with better understanding of the underlying genomic complexity of these cancers and with the implementation of advanced functional imaging techniques that identify more patients with previously occult metastatic disease. New drugs, many of which are informed by different genomic pathways, are under development (**Table 2**). Existing therapies are at the same time being used more effectively at earlier disease stages and to larger benefit. Adding to the excitement are recent efforts to incorporate locoregional therapies to improve outcomes for patients with metastatic disease. While cure is elusive, we anticipate substantial improvement in the management of patients with advanced prostate cancer as we use biomarkers in real time to predict response and expand treatment options to address the complexities of this disease.

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