clinical reviews

Recent Advances in the Management of Metastatic Prostate Cancer

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abstract

Management of metastatic prostate cancer has undergone a revolution over the past decade with the introduction of several novel agents and repurposing of others. Several clinical trials reported improved outcomes with the intensification of androgen deprivation therapy by the addition of docetaxel chemotherapy or novel hormonal agents (abiraterone, enzalutamide, or apalutamide) in the metastatic castration-sensitive state. Relugolix has been recently approved as the first oral gonadotropin-releasing hormone receptor antagonist agent with a superior cardiovascular side-effect profile, and serum testosterone suppression compared with a gonadotropin-releasing hormone agonist, leuprolide. Poly-ADP ribose polymerase inhibitors (olaparib and rucaparib) have demonstrated significant clinical benefit for patients harboring deleterious mutations in genes belonging to the homologous recombination repair pathway and have received Food and Drug Administration approval. Recently, lutetium-177-prostate-specific membrane antigen-617 with standard of care treatment has shown to improve overall survival in men with advanced-stage prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer. These recent approvals, successes, and the ongoing investigation of multiple novel agents are expected to continue to dramatically improve survival outcomes of men with metastatic prostate cancer in the coming years.

INTRODUCTION

In 2021, it is estimated that 26% of new noncutaneous cancer cases will be because of prostate cancer resulting in 11% of cancer-related deaths in the United States, making it the most common malignancy in men and the second leading cause of cancer mortality.[1] Following onset of metastatic disease, the disease is invariably fatal with a 5-year survival rate of only 30%. Furthermore, the incidence of metastatic prostate cancer seems to have increased in all races and age groups over the past decade.[1]

Herein, we discuss the most recent advances in the management of metastatic prostate cancer and highlight recently approved agents and ongoing clinical trials. We will review the mechanism of action of recently approved agents (Table 1; Fig 1). We also present principles for optimal therapy selection based on clinical and molecular criteria, current roadblocks regarding treatment intensification in the castrate-sensitive stage, and challenges with treatment sequencing. Finally, we summarize promising therapies currently under development.

METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Androgen deprivation therapy (ADT), either surgical or pharmaceutical, is the foundational approach to the treatment of prostate cancer. However, this is frequently associated with adverse reactions, which include sexual dysfunction, cardiovascular disease, diabetes, cognitive dysfunction, and decreased mineral bone density. Although use of intermittent ADT has been associated with a slightly better side-effect profile and quality of life compared with continuous ADT, it is not generally recommended for metastatic prostate cancer.[2,3]

Two open-label randomized clinical trials, CHAARTED and STAMPEDE, reported the clinical benefit of adding docetaxel to ADT in patients with metastatic castrate-sensitive prostate cancer (mCSPC). The use of upfront docetaxel was shown to improve overall survival (OS) in patients with mCSPC, especially for men with high-volume disease (presence of visceral metastases and/or ≥ 4 bone metastases with ≥ 1 metastasis not involving the axial skeleton or pelvis). In an updated analysis of the CHAARTED trial, the median OS, the primary end point, was significantly improved in the 513 patients with high-volume disease (hazard ratio [HR], 0.63; 95% CI, 0.50 to 0.79) but not in the 277 patients with low-volume disease (HR, 1.04; 95% CI, 0.70 to 1.55).[4] The STAMPEDE trial showed a benefit for both primary end points of OS (HR, 0.78; 95% CI, 0.66 to 0.93) and progression-free survival (PFS; HR, 0.61; 95% CI, 0.53 to 0.70); however, it included

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Recently Approved Agents for the Treatment of Metastatic Prostate Cancer

Agent	Trial (NCT No.)	Eligibility Criteria	Prior Docetaxel Therapy	No. of Patients Enrolled	Intervention Arm (no. of patients)	Control Arm (no. of patients)	Primary End Point					FDA Approval Date
							Primary End Point	Follow-Up Time	Intervention	Control	HR (95% CI; *P*)	
mCSPC												
Abiraterone	LATITUDE (NCT01715285)[42]	Newly diagnosed mCSPC ≥ 2 of following high-risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastasis	No	1,199	Abiraterone 1, 000 mg oral daily plus prednisone 5 mg daily plus ADT (597)	ADT (602)	Median OS	30.4 months (median)	NR	34.7 months	0.62 (0.51 to 0.76; < .001)	February 7, 2018
							Median rPFS		33 months	14.8 months	0.47 (0.39 to 0.55; *P* < .001)	
	STAMPEDE (NCT00268476)[11]	Newly diagnosed metastatic, node-positive, or high-risk locally advanced (N0M0, ≥ 2 of following:T3 or T4, Gleason score ≥ 8, and PSA ≥ 40 ng/mL), or recurrent disease after local therapy with high-risk features or metastasis	No	1,917	Abiraterone acetate 1,000 mg oral daily plus prednisolone 5 mg daily plus ADT (957)	ADT (960)	OS	3 years	83%	76%	0.63 (0.52 to 0.76; < .001)	
							Failure-free survival	3 years	75%	45%	0.29 (0.25 to 0.34; < .001)	
Enzalutamide	ENZAMET (NCT02446405)[16]	Patients with mCSPC starting first-line ADT	Allowed (up to two cycles)	1,125	Testosterone suppression plus enzalutamide (160 mg oral daily; 563)	Testosterone suppression plus standard nonsteroidal antiandrogen therapy (562)	OS	3 years	80%	72%	0.67 (0.52 to 0.86; .002; 34-month follow-up)	December 16, 2019
	ARCHES (NCT02677896)[17]	mCSPC Prior ADT allowed	Allowed	1,150	ADT plus enzalutamide (160 mg/day; 574)	ADT plus placebo (576)	Median rPFS	14.4 months (median)	NR	19 months	0.39 (0.30 to 0.50; < .001)	
Apalutamide	TITAN (NCT02489318)[13]	mCSPC Prior ADT < 6 months allowed	Allowed	1,052	ADT plus apalutamide (240 mg oral daily; 525)	ADT plus matched placebo (527)	OS	24 months	82.40%	73.50%	0.67 (0.51 to 0.89; .005)	September 17, 2019
							rPFS	24 months	68.20%	47.50%	0.48 (0.39 to 0.60; < .001)	
Relugolix	HERO (NCT03085095)[18]	Castration-sensitive prostate cancer including: Biochemical or clinical relapse following definitive treatment Newly diagnosed mCSPC Advanced localized disease unlikely to be cured by radiation or surgery. Prior ADT allowed if < 18 months and discontinued > 3 months	Not allowed	931	Relugolix (120 mg oral daily; 622)	Leuprolide (22.5 mg subcutaneous every 3 months; 308)	Sustained castration rate	48 weeks	96.70%	88.80%	Difference 7.9% (4.1 to 11.8; < .001 for superiority)	December 18, 2020

(continued on following page)

TABLE 1. Recently Approved Agents for the Treatment of Metastatic Prostate Cancer (continued)

Agent	Trial (NCT No.)	Eligibility Criteria	Prior Docetaxel Therapy	No. of Patients Enrolled	Intervention Arm (no. of patients)	Control Arm (no. of patients)	Primary End Point					FDA Approval Date
							Primary End Point	Follow-Up Time	Intervention	Control	HR (95% CI; *P*)	
mCRPC												
Cabazitaxel	PROSELICA (NCT01308580)[21]	mCRPC with prior docetaxel treatment	Required	1,200	Cabazitaxel 20 mg/m^2 IV every 3weeks plus prednisone 10 mg daily (598)	Cabazitaxel 25 mg/m^2 IV every 3 weeks plus prednisone 10 mg daily (602)	Median OS		13.4 months	14.5 months	1.024, upper boundary of the HR CI was 1.184	September 14, 2017
	CARD (NCT02485691)[45]	mCRPC Prior ≥ 3 cycles of docetaxel and progression during 12 months of treatment with abiraterone or enzalutamide	Required	255	Cabazitaxel 25 mg/m^2 IV every 3weeks plus prednisone 10 mg daily plus primary prophylactic granulocyte-colony stimulating factor (129)	Abiraterone (1, 000 mg orally once daily and oral prednisone 5 mg twice daily) or enzalutamide (160 mg orally once daily; 126)	Median rPFS	9.2 months (median)	8 months	3.7 months	0.54 (0.40 to 0.73; < .001)	
Olaparib	PROfound (NCT02987543)[32]	mCRPC Prior progression on NHT Qualifying HRR mutation in tumor tissue	Allowed	387	Olaparib (300 mg oral twice daily; 162 patients in cohort A)	Abiraterone acetate (1,000 mg oral daily) or enzalutamide (160 mg oral daily; 83 patients in cohort A)	Median rPFS in cohort A (*BRCA1/2* or *ATM* mutations)	7.5 months in the olaparib group and 5.4 months in the control group (median)	7.4 months	3.6 months	0.34 (0.25 to 0.47; < .001)	May 19, 2020
Rucaparib	TRITON2 (NCT02952534)[35]	mCRPC Progression on 1 or 2 NHT and one taxane-based therapy Qualifying HRR mutation	Required	157	Rucaparib (600 mg oral twice daily; 157)	NA	ORR	3 years	43.5% (per radiology review) in patients with *BRCA* mutations	NA	95% CI, 31.0 to 56.7	May 15, 2020
							PSA response	3 years	54.8% in patients with *BRCA* mutations	NA	95% CI, 45.2 to 64.1	

Abbreviations: ADT, androgen deprivation therapy; FDA, US Food and Drug Administration; HR, hazard ratio; HRR, homologous recombination repair; mCSPC, metastatic castrate-sensitive prostate cancer; mCRPC, metastatic castrate-resistant prostate cancer; NA, not available; NHT, novel hormonal therapy; NR, not reached; ORR, objective response rate; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

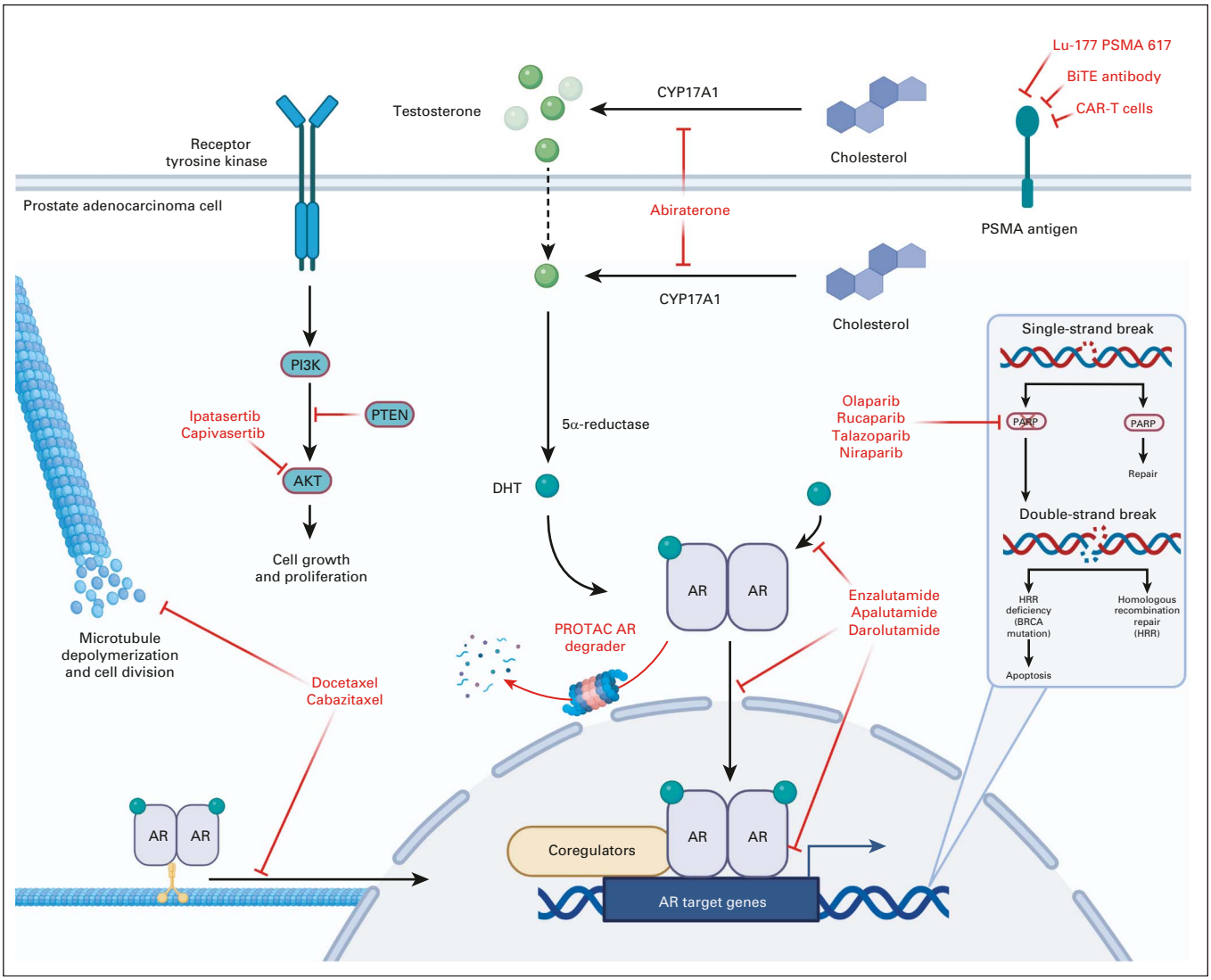

FIG 1. Targets of systemic therapies in the treatment of metastatic prostate cancer. AKT, AKR thymoma; AR, androgen receptor; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CYP17A1, cytochrome P450 17A1; DHT, dihydrotestosterone; PARP, poly ADP-ribose polymerase; PI3K, phosphoinositide 3-kinase; PROTAC, proteolysis-targeting chimera; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog. Adapted from Androgen Receptor Genomic Pathway.[53]

patients with both metastatic as well as locally advanced disease.[5] A third randomized trial, GETUG-AFU 15, demonstrated a significant improvement in secondary end points of biochemical PFS (HR, 0.67; 95% CI, 0.54 to 0.84) and radiographic PFS (rPFS; HR, 0.69; 95% CI, 0.55 to 0.87) but not for OS (HR, 0.88; 95% CI, 0.68 to 1.14), which was the primary end point. This was attributed to the small sample size (385 patients with mCSPC).[6] On a meta-analysis of these three studies, addition of docetaxel to ADT reduced all-cause death as compared to ADT alone in the overall population (HR, 0.77; 95% CI, 0.68 to 0.87), which translates into 94 fewer deaths per 1,000 men (95% CI, 51 to 137 fewer deaths).[7] In all trials, the combination of docetaxel and ADT was significantly associated with a greater frequency of adverse events of grade 3 or higher, consisting mainly of neutropenia and neuropathy.

Recent Approvals

The addition of abiraterone to ADT in patients with newly diagnosed high-risk mCSPC (defined as the presence of ≥ 2 of the following: Gleason score ≥ 8, ≥ 3 bone lesions, or presence of measurable visceral metastasis) was shown to improve OS (HR, 0.66; 95% CI, 0.56 to 0.78) as well as quality of life (QoL) in the LATITUDE trial.[8,9] Patient-reported outcomes showed a consistent benefit with the addition of abiraterone concerning pain progression, fatigue, prostate cancer symptoms, functional decline, and overall health-related QoL. This led to the US Food and Drug Administration (FDA) approving abiraterone in February of 2018 for high-risk mCSPC.[10] Similarly, in the STAMPEDE trial, the addition of abiraterone to ADT showed an OS benefit compared with ADT alone (HR, 0.63; 95% CI, 0.52 to 0.76), with an HR of 0.61 in patients with

metastatic disease and 0.75 in men with nonmetastatic disease.[11] A post hoc analysis of the STAMPEDE trial provided the rationale for using abiraterone in men with mCSPC regardless of risk stratification (OS: HR, 0.54; 95% CI, 0.41 to 0.70; 3-year failure-free survival: HR, 0.31; 95% CI, 0.25 to 0.39).[12]

In September 2019, apalutamide received FDA approval for patients with mCSPC based on results reported in the phase III TITAN trial.[10] This study enrolled 1,052 patients with mCSPC and allowed prior docetaxel. At a median follow-up of 23 months, a benefit was observed in the dual primary end points of OS (HR, 0.67; 95% CI, 0.51 to 0.89) and rPFS (HR, 0.48; 95% CI, 0.39 to 0.60). The 2-year OS was 82.4% in the apalutamide group compared with 73.5% in the ADT only group ($P = .005$).[13] Health-related QoL was maintained with time to worst pain intensity progression showing no significant difference between the two groups (HR, 0.89; 95% CI, 0.75 to 1.06).[14] In an updated analysis after a median follow-up of 44 months, the benefit in OS with apalutamide over placebo was maintained (HR, 0.65; 95% CI, 0.53 to 0.79). Remarkably, after adjustment for the crossover of 40% patients on the placebo arm to the apalutamide arm, there was an unprecedented 48% reduction in the risk of death with apalutamide (HR, 0.52; 95% CI, 0.42 to 0.64).[15]

The combination of enzalutamide and ADT in the mCSPC setting was investigated in two phase III trials: ENZAMET and ARCHES. In the ENZAMET trial, which allowed the use of concurrent docetaxel, an improvement in both PFS (HR, 0.40; 95% CI, 0.33 to 0.49) and OS (HR, 0.67; 95% CI, 0.52 to 0.86) was observed with the addition of enzalutamide at a median follow-up of 34 months as compared to the ADT with older standard-of-care antiandrogens such as bicalutamide. The combination of docetaxel and enzalutamide increased toxicities and decreased the chances of completion rate of the six planned docetaxel cycles (65% in enzalutamide *v* 76% in the standard of care group) without any significant OS improvement (HR, 0.90; 95% CI, 0.62 to 1.31, the *P* value for interaction .04, adjusted *P* value .14). Toxicities associated with enzalutamide were mainly fatigue and seizures.[16] The second trial ARCHES, which allowed prior docetaxel, has also met its primary end point of rPFS (HR, 0.39; 95% CI, 0.30 to 0.50) in both low- and high-volume disease patients.[17] These results led to the approval of enzalutamide for mCSPC by the FDA in December 2019.[10]

The latest agent to be approved for mCSPC is relugolix, a highly selective oral gonadotropin-releasing hormone receptor antagonist. The superiority of relugolix (120 mg orally daily) over leuprolide (injection every 3 months) was demonstrated in the phase III HERO trial in which 96.7% of patients maintaining castration at 48 weeks compared to 88.8% with leuprolide ($P < .001$). Furthermore, faster testosterone suppression and recovery' as well as significantly lower rates of major cardiovascular events (especially in men with prior cardiovascular events) were achieved in the relugolix arm.[18]

Ongoing Investigations

Darolutamide is currently being evaluated in combination with docetaxel and ADT versus docetaxel and ADT (ARASENS trial; NCT02799602), and in combination with ADT versus ADT alone in men with mCSPC (ARANOTE trial; NCT04736199). Capivasertib, a novel AKT inhibitor, is being investigated in combination with abiraterone in men with mCSPC with phosphatase and tensin homolog deficiency (CAPItello-281 trial, NCT04493853), whereas niraparib, a poly-ADP ribose polymerase (PARP) inhibitor, is being investigated in combination with abiraterone in men with mCSPC with homologous recombination repair (HRR) gene mutations (AMPLITUDE trial, NCT04497844). These two trials, if successful, will establish precision medicine in this space. Role of radiation therapy is discussed in the Data Supplement (online only).

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Docetaxel and cabazitaxel are both approved chemotherapeutic agents for metastatic castrate-resistant prostate cancer (mCRPC). The TAX-372 trial showed improved OS with the use of docetaxel compared with mitoxantrone in men with mCRPC after disease progression on ADT (median 19.2 *v* 16.3 months; $P = .004$).[19] TROPIC trial demonstrated benefit of cabazitaxel (25 mg/m^2) over mitoxantrone in mCRPC after progression on docetaxel in terms of OS (median 15.1 *v* 12.7 months, HR, 0.70; 95% CI, 0.59 to 0.83) and PFS (median 2.8 *v* 1.4 months, HR, 0.74; 95% CI, 0.64 to 0.86).[20] The PROSELICA trial led to the approval of a lower dosage of cabazitaxel (20 mg/m^2) and showed lower grade 3 or 4 AEs and neutropenic sepsis.[21] Nevertheless, docetaxel remains the preferred agent in chemonaïve mCRPC patients after the FIRSTANA trial failed to demonstrate the superiority of cabazitaxel over docetaxel.[22]

Abiraterone and enzalutamide have also been approved for the treatment of mCRPC. The COU-AA-301[23] and COU-AA-302[24] placebo-controlled trials have both demonstrated the survival benefit of abiraterone in docetaxel-pretreated (median OS: 14.8 *v* 10.9 months, HR, 0.65; 95% CI, 0.54 to 0.77) and chemonaïve mCRPC patients (median OS 34.7 *v* 30.3 months, HR, 0.81; 95% CI, 0.70 to 0.93), respectively. Similarly, enzalutamide is approved for both docetaxel pretreated and chemonaïve mCRPC patients through the placebo-controlled AFFIRM (median OS: 18.4 *v* 13.6 months; HR, 0.63; 95% CI, 0.53 to 0.75; $P < .001$)[25] and PREVAIL (median OS: 32.4 *v* 30.2 months; HR, 0.71; 95% CI, 0.60 to 0.84; $P < .001$)[26] trials, respectively.

Radium-223 is a radioactive isotope of radium that emits low levels of alpha-particle radiation and acts as a calcium mimetic particle that is incorporated during osteogenesis at metastatic bone lesions. In the phase III ALSYMPCA trial, radium-223 significantly improved the median OS (HR,

0.70; 95% CI, 0.58 to 0.83) and time to first skeletal event (15.6 *v* 9.8 months; $P < .01$) in patients with mCRPC as compared to placebo in all subgroups (docetaxel-naïve and exposed).[27] Based on trial criteria, radium-223 has only been approved for patients with mCRPC with symptomatic bone metastases, without evidence of visceral disease and the maximum lymph node diameter of ≤ 3 cm.

Immunotherapy with either sipuleucel-T or pembrolizumab is also an option for some patients with mCRPC. Sipuleucel-T is a dendritic cell vaccine prepared from patients' peripheral blood mononuclear cells obtained through leukapheresis. It is approved for the treatment of asymptomatic or minimally symptomatic patients with mCRPC without evidence of visceral disease.[28] Pembrolizumab is approved in a tissue agnostic manner for patients with tumors that are microsatellite instability-high (MSI-H), and/or harbor mismatch repair deficiency mutations (dMMR; found in < 3% of men with metastatic prostate cancer[29]), and/or have high tumor mutational burden (TMB ≥ 10 mutations/megabase) having progressed on prior approved therapies and have no satisfactory alternative treatment options.[30]

Recently, in men with prostate-specific membrane antigen (PSMA)-positive mCRPC who have previously been treated with novel hormonal therapy (NHT) and 1-2 taxanes, the addition of ^{177}Lu-PSMA-617 to the standard of care as compared to standard of care therapy alone has shown to significantly improve rPFS (median 8.7 *v* 3.4 months; HR, 0.40 [99.2% CI, 0.29 to 0.57]; $P < .001$, one-sided) and OS (median 15.3 *v* 11.3 months; HR, 0.62 [95% CI, 0.52 to 0.74]; $P < .001$, one-sided).[31]

Recent Approvals

PARP inhibitors block the enzymatic activity of PARP, which repair single-strand DNA breaks. These can also trap PARP in a nonactive state bound to chromatin. In patients harboring mutations in HRR genes (responsible for repairing double-strand DNA breaks), the use of PARP inhibitors leads to synthetic lethality because of concomitant deficiency in both single- as well as double-strand repair. The PROfound trial[32] was a phase III study that enrolled men with mCRPC with prior progression on NHT (enzalutamide or abiraterone or both) and randomly assigned them 2:1 to either olaparib (256 patients) or the physician's choice of NHT (131 patients). Cohort A included 245 patients with at least one alteration in *BRCA1/2* or *ATM*, whereas cohort B included 142 patients with at least one alteration in any of the other 12 prespecified genes. Olaparib significantly improved the primary end point of rPFS in cohort A (median 7.4 *v* 3.6 months, HR, 0.34; 95% CI, 0.25 to 0.47; $P < .001$). Clinical benefit was less pronounced in cohort B after including the other HRR genes in the analysis. In cohort A, olaparib also showed an OS benefit compared with the control arm (median 19.1 *v* 14.7 months; HR, 0.69; 95% CI, 0.50 to 0.97; $P = .02$), although it was not statistically significant in cohort B or overall population.[33] Remarkably, the OS benefit was maintained despite crossover of 67% patients from the control arm to the olaparib arm. After adjustment for crossover, the OS benefit with olaparib was further improved (HR, 0.42; 95% CI, 0.19 to 0.91). These results led to the approval of olaparib in May 2020 for patients with mCRPC who previously progressed on enzalutamide or abiraterone and who carry alterations (germline and/or somatic) in any of the following genes: *BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B/C/D,* and *RAD54L*.[34]

Another PARP inhibitor, rucaparib, has shown efficacy in a multicenter single-arm open-label phase II trial, TRITON2. Patients with a diagnosis of mCRPC, presence of an HRR gene mutation (*BRCA* and non-*BRCA*), and progression on one or two NHTs and taxane-based chemotherapy were eligible for the trial. In men with *BRCA1/2* mutations, objective response rate (ORR) per independent radiology review was 43.5%, prostate-specific antigen response rate was 54.8%, and median rPFS was 9.0 months (95% CI, 8.3 to 13.5 months). No difference in outcomes was observed between patients harboring germline or somatic HRR mutations.[35] Clinical benefit for patients harboring alterations in *ATM*, *CDK12*, or *CHEK2* remains unclear because of lower response rates and the limited number of patients.[36] Rucaparib received accelerated approval in May 2020 for patients with mCRPC harboring a deleterious *BRCA* mutation (germline and/or somatic) who have been treated with an androgen receptor–directed therapy and a taxane-based chemotherapy.[34]

Ongoing Investigations

The results from the ongoing phase III TRITON3 trial (NCT02975934) comparing rucaparib with abiraterone, enzalutamide, or docetaxel in patients with mCRPC with HRR deficiency are expected to lead to full FDA approval of rucaparib. Preliminary reports from two phase II trials (GALAHAD and TALAPRO-1)[37,38] show promising results for two other PARP inhibitors (niraparib and talazoparib) in patients with mCRPC with deleterious *BRCA1/2* mutations (ORR: 41% and 44%, respectively), and these two PARP inhibitors are likely going to garner regulatory approval in the near future.

SELECTION OF PATIENTS

Metastatic Castration-Sensitive Prostate Cancer

In the absence of studies comparing the different ADT combination regimens (abiraterone, enzalutamide, apalutamide, and docetaxel), several factors may be considered, such as toxicity, cost, and duration of therapy, when selecting the preferred therapy for our patient with mCSPC. A meta-analysis of seven trials suggested better OS with enzalutamide compared with docetaxel in men with low-volume disease, but there was no difference in other comparisons.[39] In a comparative subset analysis of the

STAMPEDE trial, similar OS and PFS benefit was observed with either abiraterone or docetaxel plus ADT.[40] No difference in the worse toxicity grade was noted, although global QoL was significantly higher for the abiraterone group in the first 2 years.[41]

Both docetaxel and NHT are reasonable choices for patients with high-volume disease. Side-effect profiles, comorbidities, and financial toxicity should guide management. Docetaxel is mainly associated with neuropathy, diarrhea, and neutropenia,[5] whereas abiraterone is associated with hypertension, hypokalemia, and hepatotoxicity.[42] Moreover, the administration of prednisone with abiraterone may exacerbate existing comorbidities such as diabetes, hypertension, and osteoporosis.[42] Enzalutamide may be associated with cognitive impairment, seizures, and cardiovascular disease[13,16]; however, both enzalutamide and apalutamide can be recommended regardless of disease volume. Upfront docetaxel is usually given over 15 weeks (six cycles), whereas NHT is continued over months to years and therefore can be associated with higher financial morbidity.[43] A notable advantage of apalutamide and enzalutamide over docetaxel and abiraterone is that patients do not need frequent laboratory testing or monitoring of side effects such as hypertension, which makes it more prudent to use these agents, especially during the ongoing pandemic. Concerning ADT agents, daily relugolix may be a reasonable choice for patients with cardiovascular comorbidities but is also associated with a higher financial burden compared with leuprolide. Importantly, there is no evidence supporting the safety or efficacy of combining relugolix with either docetaxel or NHT, and such combinations may be associated with serious and unpredictable drug-drug interactions.

Metastatic Castration-Resistant Prostate Cancer

Side-effect profiles, comorbidities, and cost play an important role in treatment selection for patients with mCRPC; however, some treatment sequences may be preferred. Abiraterone or enzalutamide should be considered in newly diagnosed mCRPC who have not received prior NHTs. A phase II crossover trial indicated that the use of abiraterone followed by enzalutamide was associated with a longer time to prostate-specific antigen progression compared with the reverse sequence (median 19.3 *v* 15.4 months; $P = .036$).[44] Docetaxel can be used in chemonaïve patients with good performance status and patients who did not experience disease progression while receiving docetaxel in mCSPC. Patients harboring the androgen receptor splice variant 7 (AR-V7) may be candidates for docetaxel rather than NHT.[2] Although FIRSTANA trial failed to demonstrate the superiority of cabazitaxel over docetaxel in chemonaïve mCRPC,[22] cabazitaxel has a lower risk of neuropathy and can thus be preferred over docetaxel in diabetic chemonaïve patients. The results from the CARD trial demonstrated a significant increase in median rPFS (8 *v* 3.7 months; $P < .001$) and OS (13.6 *v* 11 months; $P = .008$) for patients treated with cabazitaxel compared with a second NHT who were previously treated with docetaxel and had experienced mCRPC progression within 12 months of starting an NHT.[45] Radium-223 can be used in men with symptomatic bone metastasis and no evidence of visceral disease.[27] Sipuleucel-T is a viable alternative in asymptomatic or minimally symptomatic patients with new mCRPC and no liver metastasis after prior disease progression on ADT alone. Pembrolizumab may be used for a select few patients with either MSI-H or dMMR disease or TMB $\geq$ 10 mutations/megabase with prior disease progression on approved therapies.

PARP inhibitors should only be considered in men with an HRR deficiency. Rucaparib can only be considered in those with mCRPC harboring deleterious mutations in the *BRCA1* and/or *BRCA2* genes, and prior therapy with an NHT as well as a taxane. However, olaparib is approved for men with a wider range of HRR gene mutations and does not require prior taxane therapy.[32,35] Recently, circulating tumor DNA testing has emerged as a more attractive and a feasible alternative for the detection of tumor HRR gene alterations compared with more tedious tumor tissue testing. Additionally, germline testing is now recommended for all patients with metastatic prostate cancer after appropriate genetic counseling.[2,34]

CHALLENGES AND FUTURE DIRECTIONS

Recent advancements in the treatment paradigm have also posed new challenges in how we combine and/or sequence these therapeutic agents. With the STAMPEDE, CHAARTED, LATITUDE, TITAN, ARCHES, and ENZAMET trials showing a clear benefit for intensifying ADT with docetaxel or NHT for patients with mCSPC, the number of patients not receiving intensified treatment remains perplexingly high.[46] Another challenge is the selection and sequencing of agents in the mCRPC setting after prior disease progression on an intensified ADT regimen, as neither NHT nor taxanes (or even radium-223 or sipuleucel-T) for mCRPC were originally approved after prior intensified ADT in the mCSPC setting.

Access to newly approved NHTs as well as genetic testing will face barriers with regards to utilization in low- and middle-income countries both because of their exorbitant price as well as poor medical coverage.[47] Therefore, there needs to be a coordinated effort between various stakeholders including clinicians, pharmaceutical companies, government health agencies, patient advocacy groups, and oncology societies or cooperative groups to mitigate regulatory, financial, and cultural barriers with regards to access to these life-prolonging therapies. In this context, abiraterone 250 mg/day following a low-fat breakfast can be an alternative to the standard 1,000 mg/day abiraterone dose, which can reduce financial toxicity.[48]

TABLE 2. Selected Ongoing Trials of Interest

Trial (NCT No.)	Eligibility Criteria	Prior Docetaxel Therapy	Target Enrollment	Intervention Arm	Control Arm	Primary End Point
MAGNITUDE (NCT03748641)	mCRPC Prior systemic therapy with NHT, PARPi, or chemotherapy in the mCRPC setting not allowed	Not allowed	1,000	Niraparib (200 mg oral daily) plus abiraterone acetate (1,000 mg oral daily) plus prednisone (5 mg daily)	Placebo plus abiraterone acetate (1,000 mg oral daily) plus prednisone (5 mg daily)	rPFS in cohorts 1 (patients with HRR mutations) and cohort 3 (open label)
AMPLITUDE (NCT04497844)	mCSPC Prior abiraterone allowed for up to 30 days	Not allowed	788	Niraparib (200 mg oral daily) plus abiraterone acetate (1,000 mg oral daily) plus prednisone (5 mg daily)	Placebo plus abiraterone acetate (1,000 mg oral daily) plus prednisone (5 mg daily)	rPFS
TALAPRO (NCT03395197)	Asymptomatic or minimally symptomatic progressive mCRPC to bone or soft tissue Prior treatment with PARPi or NHT not permitted	Allowed	1,037	Talazoparib 0.5 mg/day plus enzalutamide 160 mg/day	Placebo plus enzalutamide 160 mg/day	Talazoparib dose confirmation rPFS in unselected patients and patients with HRRm
PROPEL (NCT03732820)	First-line mCRPC Prior treatment with PARPi not permitted	Allowed	904	Olaparib (300 mg twice daily) plus abiraterone acetate (1,000 mg daily)	Abiraterone acetate (1, 000 mg daily)	rPFS
TRITON3 (NCT02975934)	mCRPC Have a deleterious mutation in a BRCA1/2 or ATM gene	Not allowed (if in mCRPC setting)	400	Rucaparib	Abiraterone acetate or enzalutamide or docetaxel	rPFS
KEYLINK-010 (NCT03834519)	mCRPC (diagnosed < 6 months) Prior progression on docetaxel (mCRPC setting) and either abiraterone (mCRPC or mCSPC setting) or enzalutamide (mCRPC setting)	Required	780	Pembrolizumab plus olaparib	Abiraterone acetate or enzalutamide	OS rPFS
PEACE III (NCT02194842)	Asymptomatic or minimally symptomatic progressive mCRPC to bone Visceral metastases not allowed	Allowed	560	Ra223 (50 Bq/kg) plus enzalutamide (160 mg daily)	Enzalutamide (160 mg daily)	rPFS
IPATential150 (NCT03072238)	Asymptomatic or minimally symptomatic progressive mCRPC Prior vaccine therapy, immunotherapy, or enzalutamide not permitted Valid immunohistochemistry PTEN result	Not allowed	1,101	Ipatasertib (400 mg oral daily) plus abiraterone (1,000 mg oral daily)	Placebo plus abiraterone (1, 000 mg oral daily)	rPFS
CAPItello-281 (NCT04493853)	Asymptomatic or minimally symptomatic progressive mCRPC PTEN deficiency (immunohistochemistry)	Allowed	1,000	Capivasertib (400 mg twice daily) plus abiraterone acetate (1, 000 mg daily)	Placebo plus abiraterone acetate (1,000 mg daily)	rPFS
ARASENS (NCT02799602)	mCSPC Prior ADT not permitted	Not allowed	1,303	Darolutamide (300 mg twice daily) plus ADT plus docetaxel	Placebo plus ADT plus docetaxel	OS
S1216 (NCT01809691)	mCSPC Prior abiraterone or enzalutamide not permitted	Not allowed (except in neoadjuvant and adjuvant setting)	1,313	TAK-700 (300 mg twice daily) plus ADT	Bicalutamide (50 mg daily) plus ADT	OS

(continued on following page)

TABLE 2. Selected Ongoing Trials of Interest (continued)

Trial (NCT No.)	Eligibility Criteria	Prior Docetaxel Therapy	Target Enrollment	Intervention Arm	Control Arm	Primary End Point
TheraP (NCT03392428)	mCRPC Significant PSMA avidity on 68 Ga-PSMA PET-CT Prior treatment with cabazitaxel or Lu-PSMA not permitted	Required	201	6-8.5 GBq of ^{177}Lu-PSMA-617 intravenous every 6 weeks	Cabazitaxel (20 mg/m^2)	PSA response rate
CONTACT-02 (NCT04446117)	mCRPC Prior treatment with one, and only one, NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide)	Not allowed (except if for mCSPC)	580	Cabozantinib (40 mg orally daily) Atezolizumab (intravenous infusion once every 3 weeks)	Enzalutamide (160 mg orally daily) or abiraterone acetate (1,000 mg orally daily)	PFS OS
KEYNOTE-641 (NCT03834493)	mCRPC Prior treatment with NHT (except abiraterone), chemotherapy, radiopharmaceuticals, or immune checkpoint blockers not permitted	Not allowed	1,200	Enzalutamide plus pembrolizumab	Enzalutamide plus placebo	OS rPFS
KEYNOTE-921 (NCT03834506)	mCRPC Prior treatment with NHT Prior treatment chemotherapy, radiopharmaceuticals, or immune checkpoint blockers not permitted	Not allowed (except if for mCSPC)	1,000	Pembrolizumab plus docetaxel	Placebo plus docetaxel	OS rPFS

Abbreviations: ADT, androgen deprivation therapy; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NHT, novel hormonal therapy; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PET-CT, positron emission tomography-computed tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival.

Future directions in the management of metastatic prostate cancer include the identification of new molecular targets as well as the development of new immunotherapy combinations (Table 2). As an example, preliminary results of a placebo-controlled phase III trial evaluating the combination of abiraterone and ipatasertib (an AKT inhibitor) in patients with mCRPC are encouraging. Patients harboring a loss-of-function mutation in the *PTEN* gene by immunohistochemistry had improvement in rPFS (primary end point: HR, 0.65; 95% CI, 0.45 to 0.95; $P = .0206$) with the addition of ipatasertib to abiraterone.[49] Another example is the combination of cabozantinib (a multityrosine kinase inhibitor) and an immune checkpoint inhibitor atezolizumab. This combination demonstrated an ORR of 32% and a median duration of response of 8.3 months in a heavily pretreated population of patients with mCRPC (phase 1b COSMIC-021 trial; NCT03170960). A phase 3 CONTACT-2 trial (NCT04446117) has already been initiated with this combination.[50] More agents with novel mechanisms of action are being investigated. ARV-110, a chimeric protein promoting the ubiquitination and degradation of the androgen receptor, is an example.[51] Other promising agents include agents targeting PSMA antigen, novel radioimmune agents, monoclonal antibodies, chimeric-antigen receptor-T cells, and bispecific T-cell engagers.[52]

In conclusion, an extraordinary pace of drug development and approvals have revolutionized the treatment paradigm of metastatic prostate cancer over the past decade. The current era of targeted therapy, immunotherapy, theranostics, and the overall treatment of advanced prostate cancer will continue to evolve rapidly, and further improvements in survival outcomes are expected in the coming years. These advancements in therapeutics will also pose new challenges in the clinic in terms of treatment selection and sequencing of therapies, and will increasingly require additional studies that focus on optimization of outcomes and minimization of cost and toxicities.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Recent Advances in the Management of Metastatic Prostate Cancer

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