New Drug Approvals in Prostate Cancer and Their Effect on the Treatment Landscape

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Abstract: Prostate cancer is the most frequently diagnosed non-skin cancer and the second leading cause of cancer-related mortality in men in the United States. Over the past decade, the treatment landscape for advanced prostate cancer has rapidly shifted. For decades, androgen deprivation therapy has been the cornerstone of systemic treatment for patients with metastatic hormone-sensitive prostate cancer (mHSPC). However, more recently, we have seen the emergence of doublet and triplet combinations in the mHSPC setting. At the same time, there is an expanding list of treatments for patients with metastatic castration-resistant prostate cancer (mCRPC), including hormonal treatments, chemotherapy, immunotherapy, bone-targeted agents, radioligand therapy, and targeted therapy. The shifting of the treatment landscape for advanced prostate cancer has raised many questions regarding patient selection, therapy choice, and sequencing of different approved agents, particularly in the mCRPC setting with the earlier use of chemotherapy and androgen receptor signaling inhibitors. Since then, multiple trials have been conducted to improve the management of mHSPC and delay its progression to mCRPC. This review article discusses various clinical trials that focus on novel therapeutic targets for prostate cancer and how the initiation of newer clinical trials has affected older therapies and trials.

Keywords
Castration-resistant prostate cancer, hormone-sensitive prostate cancer, novel therapeutics, prostate cancer

Introduction

Prostate cancer is the most frequently diagnosed non-skin cancer and the second leading cause of cancer-related mortality in men in

the United States.[1] Prostate cancer is biologically heterogeneous, with varying presentations, disease states, and outcomes. Although patients with localized disease have an excellent prognosis with a 5-year relative survival of almost 100%, those with metastatic disease have a worse prognosis and no curative treatment options.[2,3] For decades, androgen deprivation therapy (ADT) has been the cornerstone of systemic treatment for patients with metastatic hormone-sensitive prostate cancer (mHSPC).[4] Castration-resistant prostate cancer (CRPC), in which the disease progresses despite medical or surgical castration, is an advanced form of prostate cancer that is often lethal when concurrent metastases are present.[5] Castration resistance is defined by a progressively rising prostate specific antigen (PSA) level and new metastasis or the progression of existing metastasis in individuals whose testosterone levels are less than 50 mg/mL owing to ADT or surgical castration.[5]

A better understanding of the factors that mediate prostate cancer progression, immune tolerance, cell proliferation, and survival has led to the development of additional therapeutic options for patients with advanced disease.[2] Even though the pathophysiology of CRPC is multifactorial, studies have shown that androgen receptor (AR) signaling remains crucial in disease progression.[6] Various adaptive mechanisms, such as increased levels of intracellular androgens, AR mutations resulting in AR activation by promiscuous ligands, AR gene amplification, and constitutively active splice variations, have been identified as mechanisms of resistance in CRPC.[7,8] AR-independent mechanisms, including signaling through the cyclin-dependent kinase/retinoblastoma pathway, the phosphoinositide 3-kinase (PI3K)/serine threonine kinase (AKT)/mammalian target of rapamycin (mTOR) pathway, Wnt signaling and DNA repair pathways are prevalent and are targets for therapeutic advances in prostate cancer.[9]

Over the past decade, the treatment landscape for advanced prostate cancer has rapidly shifted. There is now an expanding list of treatments available for patients with mCRPC, including hormonal treatments, chemotherapy, immunotherapy, radioligand therapy, bone-targeted agents, and targeted therapy. Hormonal treatments for mCRPC include abiraterone, enzalutamide (Xtandi, Astellas), apalutamide (Erleada, Janssen), and darolutamide (Nubeqa, Bayer HealthCare); chemotherapy includes docetaxel and cabazitaxel (Jevtana, Sanofi-Aventis); immunotherapy includes sipuleucel-T (Provenge, Dendreon) and pembrolizumab (Keytruda, Merck); radioligand therapy includes radium-223 (Xofigo, Bayer) and ^{177}Lu-PSMA-617 (Pluvicto, Novartis); bone-targeted agents include zoledronic acid and denosumab; and targeted agents include olaparib (Lynparza, AstraZeneca) and rucaparib (Rubraca, Clovis Oncology). The treatment options for patients with mHSPC expanded in 2015, with the earlier use of therapies previously used in the mCRPC setting being shifted to mHSPC. Before 2015, the standard treatment for mHSPC was ADT alone. However, in 2015, 2 landmark studies reported the benefit of docetaxel for patients with mHSPC. The CHAARTED and STAMPEDE (arm C) trials showed an overall survival (OS) advantage when combining the taxane chemotherapy docetaxel with ADT,[10,11] shifting the standard of care to combination treatments for mHSPC. In 2017, the STAMPEDE (arm G) and LATITUDE trials also demonstrated improved OS in patients receiving ADT combined with abiraterone.[11,12] A post hoc analysis of the 2017 STAMPEDE abiraterone comparison group showed that men with metastatic hormone-naive prostate cancer gain treatment benefit from ADT plus abiraterone and prednisolone irrespective of risk stratification or volume.[13] Additional phase 3 trials have subsequently demonstrated an OS benefit with the next-generation AR antagonists apalutamide and enzalutamide. More recently, triple therapy with ADT and docetaxel plus either abiraterone or darolutamide has emerged as a treatment option in the mHSPC setting. The results of the ARASENS and PEACE-1 trials have led to the addition of an androgen receptor signaling inhibitor (ARSI) in patients with mHSPC receiving docetaxel.[14,15] The positive results of several phase 3 studies in advanced prostate cancer have raised many questions regarding patient selection, therapy choice, and therapy sequence, particularly in the mCRPC setting, with the earlier use of chemotherapy and ARSIs. Since then, multiple trials have been conducted to improve the management of mHSPC and delay its progression to mCRPC. Despite these approvals and updated guidelines, real-world data highlight that a substantial proportion of patients with mHSPC are not receiving appropriate escalation of care.[16] This review article discusses various clinical trials focusing on newer therapeutic targets for prostate cancer and how the initiation of newer clinical trials has affected older therapies and trials.

Shifting Landscape for Treatment of Metastatic Prostate Cancer

Treatment options have broadly expanded in the last decade for patients with advanced prostate cancer, including mHSPC, nonmetastatic CRPC (nmCRPC), and mCRPC. In 1941, Huggins and Hodges revealed the therapeutic benefit of castration in prostate cancer.[17] In response, achieving castrate levels of testosterone became the pillar of treatment in patients with mHSPC, either surgically by performing bilateral orchiectomy or medically through the use of gonadotropin-releasing hormone analogues that suppresses the synthesis of testicular androgens.[18] During the past decades, trials were conducted to escalate and intensify treatment for mHSPC to improve

patient survival. Several systemic therapies, including docetaxel chemotherapy and second-generation ARSIs (eg, abiraterone, apalutamide, and enzalutamide), were studied in the setting of mHSPC, with ADT remaining the mainstay of treatment. Docetaxel was studied in patients with mHSPC in the CHAARTED trial,[10] which showed that adding docetaxel to ADT increased OS by 13.6 months (hazard ratio [HR], 0.61; 95% CI, 0.47-0.80). Outcomes were stratified by the volume of disease. Although there was no OS benefit for low-volume prostate cancer (HR, 1.04; 95% CI, 0.50-0.79), there was a significant benefit for patients with high-volume disease (HR, 0.63; 95% CI, 0.50-0.79).[19] Similarly, arm C of the STAMPEDE trial showed that docetaxel combined with ADT increased median OS by 10 months (HR, 0.78; 95% CI, 0.66-0.93) in patients with and without metastatic disease, further validating the addition of docetaxel for patients with HSPC.[11] Based on the results of these trials, the combination of docetaxel and ADT has become the standard of care for relatively fit men with mHSPC, especially those with a high burden of metastatic disease.[18]

Sequential to the investigation of docetaxel in mHSPC, the addition of an ARSI to ADT was tested in patients with mHSPC. Abiraterone was approved by the US Food and Drug Administration (FDA) in February 2018 for patients with mHSPC following the results of 2 clinical trials. The LATITUDE trial showed that the combination of abiraterone and ADT increased OS in patients with mHSPC with high-risk prostate cancer after a median follow-up of 51.8 months (HR, 0.66; 95% CI, 0.56-0.78).[20] Similarly, arm G of the STAMPEDE trial revealed the OS benefit of adding abiraterone to ADT vs ADT and placebo (HR, 0.63; 95% CI, 0.52-0.76).[21] In 2019, the FDA expanded the approval of enzalutamide, a potent ARSI already approved in patients with mCRPC, to the setting of mHSPC. The ARCHES trial revealed that the combination of ADT and enzalutamide improved OS vs ADT and placebo (HR, 0.66; 95% CI, 0.53-0.81).[22] Also, the ENZAMET trial compared the combination of ADT and enzalutamide vs ADT and a nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide) and demonstrated an increased OS in the enzalutamide arm (HR, 0.67; 95% CI, 0.52-0.86). Of note, the ENZAMET trial allowed concurrent use of docetaxel at the treating clinician's discretion, given the shifting mHSPC landscape. A total of 65% of patients in the enzalutamide group received docetaxel. The analysis showed there was no evidence that docetaxel improved outcomes in those receiving enzalutamide. However, subgroup analyses using docetaxel are associated with bias and should be interpreted cautiously.[23] Apalutamide received FDA approval in 2019 based on the results of the TITAN study, which showed an increase in OS with the addition of apalutamide to ADT (HR, 0.67; 95% CI, 0.51-0.89).[24]

Although doublet therapy was shown to increase the survival of patients with mHSPC, given the distinct mechanisms of action, independent single-agent activity, nonoverlapping toxicity profile, and risk of progression despite doublet therapy in a large portion of patients, there was interest in testing the activity of docetaxel combined with an ARSI in the mHSPC setting.[18]

The ARASENS study demonstrated that the combination of ADT and docetaxel plus darolutamide reduced the mortality risk by 32% compared with ADT and docetaxel alone in patients with mHSPC (HR, 0.68; 95% CI, 0.57-0.80).[14] Similarly, the PEACE-1 trial showed that ADT and docetaxel plus abiraterone increased OS compared with ADT and docetaxel alone in both high- and low-volume groups of patients with mHSPC, although it was underpowered to show a significant benefit in those with low-volume disease.[15] Based on these data, guideline panels have recommended the addition of an ARSI in patients with mHSPC receiving docetaxel.[14,15] More work is ongoing to identify which patients with mHSPC might benefit from triple therapy. No study to date has directly compared triple therapy with ADT, docetaxel, and an ARSI vs ADT and an ARSI.

In the setting of nmCRPC, several clinical trials have demonstrated the benefit of next-generation ARSIs in men with nmCRPC who have a PSA doubling time of less than 10 months while on continuous ADT.[14,25,26] The PROSPER trial tested enzalutamide and revealed a median metastasis-free survival of 36.6 months with enzalutamide vs 14.7 months with placebo (HR, 0.29; 95% CI, 0.24-0.35).[25] The SPARTAN trial proved that median metastasis-free survival was higher with apalutamide than with placebo, at 40.5 vs 16.2 months, respectively (HR, 0.28; 95% CI, 0.23-0.35).[26] The ARAMIS trial revealed a superiority of darolutamide vs placebo in prolonging median metastasis-free survival (40.4 vs 18.4 months; HR, 0.80; 95% CI, 0.70-0.91) in addition to increasing OS.[27-30] Thus, the National Comprehensive Cancer Network (NCCN) guidelines recommend using enzalutamide, apalutamide, or darolutamide in addition to ADT in patients with nmCRPC and a PSA doubling time less than 10 months.[31] Although a direct comparison of all 3 ARSIs (enzalutamide, apalutamide, and darolutamide) is lacking, the factors that help decide the best agent in the nmCRPC setting include patient comorbidities, treatment toxicities, drug interactions, and cost.[32]

Few studies have compared the appropriate sequence of agents in the mCRPC setting. The CARD trial highlighted that using cabazitaxel results in superior survival compared with a sequential ARSI (abiraterone or enzalutamide) in patients with mCRPC previously treated with docetaxel and the alternative ARSI. Cabazitaxel increased median OS to 13.6 months compared with 11.0 months with an ARSI (HR, 0.64; 95% CI, 0.46-0.89),

Table 1. Completed Trials of Systemic Treatments for the Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary endpoint	Primary endpoint results	N	Y of completion
Docetaxel								
STAMPEDE (arm C vs arm A)	Advancing or metastatic PC	NCT00268476 [11,21]	2/3	Arm C (docetaxel + SOC/ADT) vs arm A (SOC/ADT)	OS	81 vs 71 mo, HR 0.78, 95% CI 0.66-0.93, *P*=.006[11]	12,200	2024
GETUG AFU15	mHSPC	NCT00104715 [105]	3	Docetaxel + ADT vs ADT	OS	58.9 vs 54.2 mo, HR 1.01, 95% CI 0.75-1.36	385	2004
CHAARTED	mHSPC	NCT00309985	3	Docetaxel + ADT vs ADT	OS	57.6 vs 44.0 mo, HR 0.61, 95% CI 0.47-0.80, *P*<.001[10,19]	790	2022
S9916	mCRPC	NCT00004001	3	Docetaxel (D) + prednisone (P) vs mitoxantrone (M) + prednisone; D3P arm (3 wk of D with P); D1P arm (1 wk of D with P); MP arm	OS	17.5 vs 15.6 mo, HR for death 0.80, 95% CI 0.67-0.97[36]	674	2007
TAX 327	mCRPC		3	Docetaxel (D) + prednisone (P) vs mitoxantrone (M) + prednisone; D3P arm (3 wk of D with P); D1P arm (1 wk of D with P); MP arm	OS	D3P vs D1P vs MP arms: 19.2 vs 17.8 vs 16.3 mo, HR of D3P vs MP (HR 0.79, 95% CI 0.67-0.93, *P*=.004), HR of D1P vs MP (HR 0.87, 95% CI 0.74-1.02, *P*=.086)[106]	1006	2007
Cabazitaxel								
TROPIC	mCRPC, post docetaxel	NCT00417079	3	Cabazitaxel + prednisone vs mitoxantrone + prednisone	OS	15.1 vs 12.7 mo, HR for death 0.70, 95% CI 0.59-0.83, *P*<.0001[38]	755	2009
CARD	mCRPC, post docetaxel and ARSI	NCT02485691	4	Cabazitaxel + prednisone vs ARSI (enzalutamide or abiraterone + prednisone)	Imaging-based PFS	8.0 vs 3.7 mo HR 0.54, 95% CI, 0.40-0.73, *P*<.001[33]	255	2021
Abiraterone								
STAMPEDE (arm G vs arm A)	Hormone-naive PC	NCT00268476 [11, 21]	2/3	Arm G (abiraterone + prednisone + SOC/ADT) vs arm A (SOC/ADT)	OS	3-y survival of 83% vs 76% HR 0.63, 95% CI 0.52-0.76, *P*<.001[18]	12,200	2024

Table 1. *(Continued)* Completed Trials of Systemic Treatments for the Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary endpoint	Primary endpoint results	N	Y of completion
Abiraterone								
PEACE 1	mHSPC, de novo	NCT01957436	3	SOC (ADT alone or with docetaxel) vs SOC + radiotherapy vs SOC + abiraterone + prednisone vs SOC + radiotherapy + abiraterone	Overall population: rPFS, OS	rPFS: SOC + abiraterone vs SOC (ADT alone), 4.47 vs 2.22 y (HR 0.54, 99.9% CI 0.41-0.71, *P*<.0001), OS: 5.72 vs 4.72 y (HR 0.82, 95.1% CI 0.69-0.98, *P*=.030)	1173	2018
					ADT + docetaxel population: rPFS, OS	rPFS: 4.46 vs 2.03 y (HR 0.50, 99.9% CI 0.34-0.71, *P*<.001), OS: NR vs NR (HR 0.75, 95.1% CI, 0.59-0.95, *P*=.017)[15]		
LATITUDE	mHSPC, high-risk	NCT01715285	3	Abiraterone + prednisone + ADT vs placebo + ADT	OS	53.3 vs 36.5 mo, HR 0.66, 95% CI 0.56-0.78, *P*<.0001[20]	1199	2022
COU-AA-302	mCRPC, chemotherapy-naive (asymptomatic or mildly symptomatic patients with mCRPC)	NCT00887198	3	Abiraterone + prednisone vs placebo + prednisone	OS	NR vs 27.2 mo, HR 0.75, 95% CI 0.61-0.93, *P*=.01	1088	2017
					PFS	16.5 vs 8.3 mo, HR 0.53, 95% CI 0.45-0.62, *P*<.001[107]		
COU-AA-301	mCPRC, post docetaxel (mCRPC that has failed to responds to 1 or 2 chemotherapy regimens)	NCT00638690	3	Abiraterone + prednisone vs placebo + prednisone	OS	14.8 vs 10.9 mo HR 0.65, 95% CI 0.54-0.77, *P*<.001[39]	1195	2009

Table 1. *(Continued)* Completed Trials of Systemic Treatments for the Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary end-point	Primary endpoint results	N	Y of com-pletion
Enzalutamide								
ARCHES	mHSPC	NCT02677896	3	Enzalutamide + ADT vs placebo + ADT vs placebo	rPFS	Not reached vs 19.0 mo, HR 0.39, 95% CI 0.30-0.50, *P*<.001[108]	1150	2018
ENZAMET	mHSPC	NCT02446405	3	Enzalutamide + ADT vs conven-tional nonsteroidal antiandrogen + ADT	OS	OS at 3 y: 80% vs 72%, HR 0.67, 95% CI 0.52-0.86, *P*=.002[23]	1125	2017 (Pri-mary analy-sis)
PROSPER	nmCPRC	NCT02003924	3	Enzalutamide + ADT vs placebo + ADT	OS	67.0 vs 56.3 mo, HR 0.73, 95% CI 0.61-0.89, *P*=.001[28]	1401	2023
AFFIRM	mCPRC, chemothera-py-naive	NCT00974311	3	Enzalutamide + ADT vs placebo + ADT	OS	18.4 vs 13.6 mo, HR 0.63, 95% CI 0.53-0.75, *P*<.001[40]	1199	2017
PREVAIL	mCRPC, post docetaxel	NCT01212991	3	Enzalutamide + ADT vs placebo + ADT	OS	36 vs 31 mo, HR 0.83, 95% CI 0.75-0.93, *P*<.001[57]	1717	2019
Apalutamide								
TITAN	mHSPC	NCT02489318	3	Apalutamide + ADT vs placebo + ADT	OS	OS at 24 mo, 82.4% vs 73.5% HR 0.67, 95% CI 0.51-0.89, *P*=.005[24]	525	2020
SPARTAN	nmCRPC	NCT01946204	3	Apalutamide + ADT vs placebo + ADT	MFS	40.5 vs 16.2 mo, HR 0.28, 95% CI 0.23-0.35, *P*<.001[26]	1207	2022
Darolutamide								
ARASENS	mHSPC	NCT02799602	3	Darolutamide + ADT + docetaxel vs placebo + ADT + docetaxel	OS	OS at 4 y was 62.7% vs 50.4%, HR 0.68, 95% CI 0.57-0.80, *P*<.001[14]	1303	2021
ARAMIS	nmCRPC	NCT02200614	3	Darolutamide + ADT vs placebo + ADT	MFS	40.4 vs 18.4 mo, HR 0.41, 95% CI 0.34-0.50, *P*<.001[30]	1509	2021
Sipuleucel-T								
IMPACT	mCRPC (minimally symptomatic, no visceral metastases)	NCT00065442	3	Sipuleucel-T + ADT vs placebo + ADT	OS	25.8 vs 21.7 mo HR 0.78, 95% CI 0.61-0.98[41]	512	2009

Table 1. *(Continued)* Completed Trials of Systemic Treatments for the Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary endpoint	Primary endpoint results	N	Y of completion
Radium-223								
ALSYMPCA	mCRPC	NCT00699751	3	Radium-223 + SOC vs placebo + SOC	OS	14.9 vs 11.3 mo, HR 0.70, 95% CI 0.58-0.83, *P*<.001[43]	921	2014
^{177}Lu-PSMA-617								
VISION	mCPRC, post chemotherapy and ARSI	NCT03511664	3	^{177}Lu-PSMA-617 + SOC vs SOC	OS	15.3 vs 11.3 mo, HR 0.62, 95% CI 0.52-0.74, *P*<.001	831	2023
					Imaging-based PFS	8.7 vs 3.4 mo, HR 0.40, 99.2% CI 0.29-0.57, *P*<.001[35]		
TheraP	mCRPC, post docetaxel	NCT03392428	2	^{177}Lu-PSMA-617 vs cabazitaxel	PSA response rate	65% vs 37% PSA responses (95% CI 16-42), *P*<.0001[109]	200	2021
PARP inhibitors								
PROPEL	mCRPC, ARSI-naive (first-line)	NCT03732820	3	Olaparib + abiraterone + prednisone vs placebo + abiraterone + prednisone	rPFS	24.8 vs 16.6 mo, HR 0.66, 95% CI 0.54-0.81, *P*<.0001[78]	796	2022
MAGNITUDE	mCRPC, ARSI-naive (first-line)	NCT03748641	3	Niraparib + abiraterone + prednisone vs abiraterone + prednisone	rPFS	16.6 vs 10.9 mo, HR 0.73, 95% CI 0.56-0.96, *P*=.0271[79]	765	2027
PROFOUND	mCRPC, post-ARSI	NCT02987543	3	Olaparib vs enzalutamide or abiraterone + prednisone	rPFS	7.4 vs 3.6 mo, HR 0.34, 95% CI 0.25-0.47, *P*<.001[110]	387	2022
Triton2	mCPRC, associated with DDR deficiency post 1 line of chemotherapy and 1-2 lines of ARSI	NCT02952534	2	Rucaparib	ORR	43.5%[44]	115	2021

ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitors; D, docetaxel; DDR, DNA damage repair genes; HR, hazard ratio; mCPRC, metastatic castration-resistant prostate cancer; M, mitoxantrone; MFS, metastasis-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; mo, months; ORR, objective response rate; OS, overall survival; P, prednisone; PARP, poly(ADP-ribose) polymerase; PC, prostate cancer; PFS, progression-free survival; rPFS, radiographic PFS; PSA, prostate-specific antigen; SOC, standard of care; y, year(s).

and increased the median progression-free survival (PFS) to 4.4 months compared with 2.7 months with an ARSI (HR, 0.52; 95% CI, 0.40-0.68).[33] This study highlights that a sequential ARSI in patients previously progressing on an ARSI within 12 months is not an optimal strategy for patients with mCRPC who previously progressed on docetaxel. This finding was reinforced by looking at the control arm of the PROFOUND trial, although this trial was conducted in a biomarker population. The PROFOUND trial showed that in patients with mCRPC and at least 1 alteration in *BRCA1*, *BRCA2*, or *ATM,* and progression while on previous treatment with an ARSI, the use of olaparib increased OS to 19.1 months compared with 14.7 months with the use of the alternative ARSI (HR, 0.69; 95% CI, 0.50-0.97).[34] Furthermore, many of the trials resulting in the approval of agents for mCRPC were conducted before 2015, when treatment intensification was not the standard in mHSPC (eg, docetaxel, abiraterone, enzalutamide, sipuleucel-T, radium-223, and cabazitaxel). The PROFOUND, CARD, and VISION trials had variable enrollment periods, but all accrued patients following 2015.[33-35]

Individual Agents

Multiple FDA-approved drugs have been shown to improve OS in the setting of CRPC. These drugs include 2 chemotherapeutic agents (docetaxel and cabazitaxel),[36-38] 2 ARSIs (abiraterone and enzalutamide)[39,40] 2 immunotherapeutic agents (sipuleucel-T and pembrolizumab for patients whose tumors have microsatellite instability or a high tumor mutation burden),[41,42] 2 radiopharmaceutical agents (radium-223 and ^{177}Lu-PSMA-617),[35,43] and 2 poly(ADP-ribose) polymerase (PARP) inhibitors (olaparib and rucaparib).[34,44] The expansion of the therapeutic arsenal has led to questioning the appropriate use and optimal sequencing of these new drugs. Thus, these agents were explored in several randomized controlled trials and retrospective studies. Tables 1, 2, and 3 reference current ongoing as well as completed trials of systemic treatments for the management of advanced or metastatic prostate cancer.

In 2004, the FDA approved docetaxel chemotherapy, which became the standard of care for patients with mCRPC following the TAX 327 trial showing that docetaxel improved OS when compared with mitoxantrone (18.9 vs 16.5 months; HR, 0.76; 95% CI, 0.62-0.94).[37] The combination of docetaxel and estramustine also improved OS compared with mitoxantrone (17.5 vs 15.6 months, respectively; HR, 0.80; 95% CI, 0.67-0.97).[36] Although docetaxel is now approved in both the mCRPC and mHSPC settings, it is underutilized in clinical practice.[45] This agent remains a highly effective treatment strategy, and there are strategies to ensure tolerance to treatment, including dose reductions, altered scheduling, the use of granulocyte colony–stimulating factors as indicated, and supportive care.

Cabazitaxel chemotherapy was FDA approved in 2010 for patients with mCRPC that progressed after docetaxel treatment, following the results of the TROPIC trial that revealed an increase in OS with cabazitaxel vs mitoxantrone (15.1 vs 12.7 months, respectively; HR, 0.70; 95% CI, 0.59-0.83).[38] In addition, the FIRSTANA study did not show an improvement in OS or PFS when using cabazitaxel vs docetaxel in patients with chemotherapy-naive mCRPC.[46] Also, cabazitaxel was compared with ARSI (abiraterone or enzalutamide) in the CARD trial, as highlighted earlier.[33]

Abiraterone is a P450 c17 (CYP17) inhibitor that blocks testosterone production in the testis, the adrenal glands, and the tumor itself.[47-49] The FDA first approved abiraterone in 2011 for use in patients with mCRPC who have been previously treated with docetaxel, following the COU-AA-301 trial that revealed an improved OS compared with placebo (14.8 vs 10.9 months, respectively; HR, 0.65; 95% CI, 0.54-0.77).[39] In the subsequent COU-AA-302 trial, OS was significantly higher with abiraterone than with placebo in chemotherapy-naive patients with mCRPC, at 34.7 vs 30.3 months, respectively (HR, 0.81; 95% CI, 0.70-0.93.[50] Since then, abiraterone has moved into the therapeutic arsenal for patients with mHSPC or high-risk localized prostate cancer who receive external beam radiation therapy plus ADT.[51,52] The STAMPEDE trial of abiraterone included men with locally advanced and metastatic prostate cancer; local radiotherapy was required for patients with node-negative, nonmetastatic disease and was encouraged for high-risk patients with positive nodes. The results revealed that the addition of abiraterone and prednisolone to ADT significantly increased the rates of overall and failure-free survival compared with ADT alone.[21] Frequent side effects of abiraterone are related to the underlying mechanism of action of the agent, which can result in mineralocorticoid excess, hypertension, edema, hypokalemia, and the need for concurrent corticosteroids to mitigate these side effects. Additionally, the use of abiraterone risks worsening liver function and requires laboratory monitoring.

Enzalutamide is a potent ARSI that prevents androgens from binding to the AR, translocating to the nucleus, and binding with androgen response elements to promote transcription of androgen-regulated genes.[53-56] It was approved by the FDA in 2012 for patients with mCRPC after progression on docetaxel following the results of the AFFIRM trial concluding that enzalutamide improved OS compared with placebo (18.4 vs

13.6 months, respectively; HR, 0.63; 95% CI, 0.53-0.75).[40] In the subsequent PREVAIL trial, enzalutamide demonstrated improved OS (HR, 0.71; 95% CI, 0.60-0.84) compared with placebo in chemotherapy-naive patients with mCRPC.[57] This agent was tested in the mHSPC setting in the ARCHES and ENZAMET trials, as well as in the nmHSPC setting in the PROSPER trial. Other AR inhibitors that have been tested include apalutamide in the mHSPC setting in the TITAN trial[24] and darolutamide in the nmCRPC setting in the ARAMIS trial[14] and the mHSPC setting in combination with chemotherapy in the ARASEN study.[14] Although there are many similarities between the ARSIs, there are differences in drug-drug interactions and side effects that affect patient treatment selection.[58]

Sipuleucel-T is an autologous dendritic-cell vaccine. The patient's dendritic cells are collected through leukapheresis, then exposed to a recombinant fusion human protein consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor, and reinfused into the patients for 3 doses.[59,60] This agent was FDA approved in 2010 based on the results of the IMPACT study, which demonstrated a 4.1-month OS advantage when using sipuleucel-T compared with placebo (25.8 vs 21.7 months; HR, 0.78; 95% CI, 0.61-0.98).[41] However, sipuleucel-T has been underused clinically based on several factors, including a lack of objective response, a lack of PSA response, the complex logistics of treatment administration, and cost.[61,62] Of note, sipuleucel-T has been approved for treating asymptomatic or minimally symptomatic chemotherapy-naive patients with low tumor burden mCRPC without evidence of visceral disease.[63]

Radium-223 is an alpha-emitting radioisotope that selectively targets bone.[60] The ALSYMPCA trial demonstrated a significant OS benefit in the radium-223 group compared with the placebo group (14.9 vs 11.3 months; HR, 0.70; 95% CI, 0.58-0.83).[43] This agent was FDA approved in 2013 for patients with mCRPC with bone metastases without regard to prior docetaxel use. A small retrospective study demonstrated improved activity before docetaxel therapy and in patients with asymptomatic bone disease.[64] However, further studies are needed to understand its role before chemotherapy in this group of patients. Although both sipuleucel-T and radium-223 failed to improve objective imaging and PSA response, a study suggested greater clinical activity when combining these agents in men with asymptomatic mCRPC to the bone.[65] The ERA 223 study examined the addition of radium-223 to abiraterone. The combination increased the frequency of bone fractures without improving the symptomatic skeletal related event-free survival in patients with mCRPC compared with a placebo.[66] In response to the ERA-223 trial findings, the FDA recommended against the use of radium-223 with concurrent abiraterone. Ongoing trials are exploring the use of radium-223 in combination treatments in mCRPC, such as the phase 3 DORA trial (in combination with docetaxel; NCT03574571), the phase 1/2 COMRADE trial (in combination with olaparib; NCT03317392), and the phase 3 PEACE-3 trial (enzalutamide in combination with a bone-targeted agent; NCT02194842). Preliminary results from the phase 1 portion of the COMRADE trial have demonstrated the recommended phase 2 dosing and early initial activity. In the ongoing DORA trial, preliminary results have shown that radium-223 plus docetaxel leads to more durable PSA suppression than docetaxel alone in mCRPC (NCT03574571).[67]

^{177}Lu-PSMA-617 is a targeted beta-emitting radionuclide selectively targeting prostate-specific membrane antigen (PSMA)-positive cells and their microenvironment.[68-70] The FDA approved this agent in March 2022 for patients with PSMA-positive mCRPC who have received a prior ARSI and taxane chemotherapy.[71] The approval followed the results of the VISION trial, which demonstrated that adding ^{177}Lu-PSMA-617 to the standard therapy (bisphosphonates, radiotherapy, denosumab, corticosteroid, or ARSI) increased imaging-based PFS (8.7 vs 3.4 months; HR, 0.40, 99.2% CI, 0.29-0.57) and OS (15.3 vs 11.3 months; HR, 0.62; 95% CI, 0.52-0.74) when compared with standard therapy alone.[35] In addition, the TheraP trial showed that ^{177}Lu-PSMA-617 engendered higher PSA response rates and reduced adverse events compared with cabazitaxel.[72] Currently, two phase 3 trials are exploring the use of ^{177}Lu-PSMA-617 in an earlier setting. The PSMAfore trial is investigating the use of ^{177}Lu-PSMA-617 in taxane-naive patients with mCRPC compared with a change in ARSI (NCT04689829). Preliminary data demonstrate that this study achieved its primary endpoint of improved PFS with ^{177}Lu-PSMA-617 before chemotherapy.[73] The PSMAddition trial is exploring the combination of ^{177}Lu-PSMA-617 plus the standard of care vs the standard of care alone in patients with mHSPC (NCT04720157). These trials will affect the treatment landscape and sequence of therapies in metastatic prostate cancer. Also, given this drug's mechanism of action, ^{177}Lu-PSMA-617 requires an interdisciplinary collaboration among doctors from different specialties, including medical oncologists, nuclear medicine physicians, and radiation oncologists.

PARP inhibitors can induce "synthetic lethality" by inhibiting the enzymes necessary for DNA integrity, thus leading to overwhelming DNA damage and cell death.[74,75] Two PARP inhibitors, olaparib and rucaparib, are approved by the FDA for the treatment of mCRPC in biomarker-selected populations.[76] The phase 3 PROFOUND trial compared olaparib with physician's choice

Table 2. Future Trials of Systemic Treatments for Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary endpoint	N	Y of completion
CAPItello-281	De novo mHSPC characterized by PTEN deficiency	NCT04493853	3	Capivasertib + abiraterone vs placebo + abiraterone	rPFS	1000	2026
PSMAddition	mHSPC	NCT04720157	3	^{177}Lu-PSMA-617 + SOC vs SOC	rPFS	1126	2026
Cyclone 3	High-risk mHSPC	NCT05288166	2	Abemaciclib + abiraterone + prednisone/prednisolone vs placebo + abiraterone + prednisone/prednisolone	rPFS	900	2025
TALAPRO-3	DDR-deficient mHSPC	NCT04821622	3	Talazoparib + enzalutamide vs placebo + enzalutamide	rPFS	550	2024
Amplitude	Participants with deleterious germline or somatic HRR gene-mutated mHSPC	NCT04497844	3	Niraparib + abiraterone + prednisone vs abiraterone + prednisone	rPFS	788	2024
AlphaBet (^{177}Lu-PSMA-617 and radium-223 in mCRPC)	mCRPC	NCT05383079	1/2	^{177}Lu-PSMA-617 and radium-223	DLTs, MTD, recommended phase 2 dose, 50% PSA response rate	36	2026
PSMAfore	Progressive mCRPC, taxane-naive, prior ARSI, PSMA positive disease	NCT04689828		^{177}Lu-PSMA-617 vs alternative ARSI	rPFS	470	2025
DORA	mCRPC	NCT03574571	3	Radium-223 + docetaxel vs docetaxel	OS	738	2024
Peace 3	mCRPC, asymptomatic or minimally symptomatic mCRPC with bone metastases	NCT02194842	3	Radium-223 + enzalutamide vs enzalutamide	rPFS	416	2024
COMRADE	mCRPC with bone metastasis	NCT03317392	1/2	Radium-223 + olaparib vs radium-223	Maximum tolerated dose of olaparib and radium-223, rPFS	133	2023
TRITON-3	mCRPC	NCT02975934	3	Rucaparib vs treatment with the physician's choice of abiraterone, enzalutamide, or docetaxel	rPFS	405	2023

Table 2. *(Continued)* Future Trials of Systemic Treatments for Management of Advanced or Metastatic Prostate Cancer

Trial	Condition	Identifier	Phase	Intervention	Primary endpoint	N	Y of completion
Arvinas Androgen Receptor, Inc.	mCRPC	NCT03888612	1/2	ARV-110	Safety, tolerability, pharmacokinetics, and pharmacodynamics of ARV-110	250	2023
Cyclone 2	mCRPC	NCT03706365	2/3	Abemaciclib + abiraterone + prednisone vs placebo + abiraterone + prednisone	rPFS	350	2023

ARSI, androgen receptor signaling inhibitor; DDR, DNA damage repair gene; DLTs, dose-limiting toxicities; HRR, homologous recombination repair; mCPRC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; rPFS, radiographic PFS; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; y, year.

of abiraterone or enzalutamide in patients with mCRPC that had progressed on a prior ARSI. The study enrolled patients in 2 cohorts based on their qualifying homologous recombination repair (HRR) gene alteration (cohort 1: *BRCA1*, *BRCA2*, and *ATM*; cohort 2: 12 other prespecified HRR genes). In patients with at least 1 alteration in *BRCA1*, *BRCA2*, or *ATM*, the use of olaparib increased OS compared with the alternative ARSI (19.1 vs 14.7 months; HR, 0.69; 95% CI, 0.50-0.97). For cohort B, olaparib did not show an increase in the median duration of OS (14.1 vs 11.5 months; HR, 0.96; CI, 0.63-1.49).[34] Additionally, the single-arm phase 2 TRITON trial tested the efficacy of rucaparib in patients with mCRPC that had progressed on prior taxane-based chemotherapy and at least 1 ARSI. Rucaparib demonstrated an objective response rate of 43.5% and a PSA response rate of 54.8% in patients with mCRPC and *BRCA1* or *BRCA2* mutations.[44] The ongoing TRITON3 study is investigating the use of rucaparib in mCRPC compared with abiraterone, enzalutamide, or docetaxel (NCT02975934). In a recent news release regarding the TRITON-3 trial, median radiographic PFS was longer with rucaparib vs the control treatment in the *BRCA*-mutated subgroup (11.2 vs 6.4 months, respectively) as well as in the intention-to-treat group, which included patients with a *BRCA* or *ATM* mutation (10.2 vs 6.4 months).[77] More recently, the PROPEL and MAGNITUDE studies explored the combination of a PARP inhibitor and abiraterone in an unselected patient population. Both studies were conducted in patients who had not received an ARSI for mHSPC. A primary analysis of the PROPEL trial revealed that olaparib plus abiraterone significantly increased radiographic PFS compared with abiraterone plus placebo (13.8 vs 8.2 months; HR, 0.65; 95% CI, 0.44-0.97) when administered as first-line treatment in mCRPC, regardless of HRR gene mutation status.[78] However, the addition of abiraterone also led to significantly higher toxicity than in the placebo group, at 54% vs 28%, respectively. It is important to note that PROPEL only evaluated HRR status retrospectively.[78] The MAGNITUDE trial (NCT03748641) had a slightly different trial design, enrolling patients in biomarker-positive and biomarker-negative cohorts. The study demonstrated that adding the combination of abiraterone reduced the risk of mCRPC progression by 47% compared with abiraterone alone, at 16.6 vs 10.9 months, respectively, but only in patients with HRR gene mutations.[79] Additionally, the TALAPRO-2 trial of enzalutamide plus talazoparib in unselected patients (regardless of HRR gene mutations) with mCRPC was reported to be positive.[80] Recent data from TALAPRO-2 showed that the median radiographic PFS was significantly long in the treatment arm (talazoparib + enzalutamide) than in the control arm (placebo + enzalutamide), at not reached vs 21.9 months, respectively (HR, 0.63; 95% CI, 0.51-0.78; $P<.001$). It also showed that PFS was significantly improved in HRR-deficient (HR, 0.46; 95% CI, 0.30-0.70; $P<.001$), HRR-nondeficient or unknown (HR, 0.70; 95% CI, 0.54-0.89; $P=.004$), and HRR-nondeficient patients by tumor tissue testing (HR, 0.66; 95% CI, 0.49-0.91; $P=.009$) in the treatment arm.[81] Although the combination of olaparib and abiraterone was approved in the European Union in December 2022, it is still under consideration in the United States. As the frequency of individuals receiving escalated therapy in the mHSPC is increasing, the application to clinical practice

Table 3. Therapeutics for Metastatic Prostate Cancer

Agent	Mechanisms of action	Indications
Docetaxel	Inhibition of microtubular polymerization, attenuation of BCL2 and BCL-XL expression	mHSPC with ADT and enzalutamide, docetaxel-naive mCRPC
Cabazitaxel	Microtubule inhibitor	mCRPC refractory to docetaxel
Enzalutamide	Threefold inhibitor of androgen signaling pathway: inhibits androgen binding to the receptor, AR translocation to the nucleus, and interaction of the AR with the nucleus	mHSPC with ADT, non-naive and naive mCRPC
Apalutamide		mHSPC with ADT
Darolutamide		mHSPC with chemotherapy, mHSPC with ADT
Abiraterone	Androgen biosynthesis inhibitor	Newly diagnosed high-risk mHSPC with ADT, mCRPC with docetaxel
Radium-223	Alpha-emitting radioisotope selectively binding to bone with increasing turnover, leading to double-strand DNA breaks and cell death	mCRPC with bone metastasis
^{177}Lu-PSMA-617	Beta-emitting radionuclide targeting PSMA on prostate cells and their microenvironment	mCRPC refractory to previous treatment with ADT or taxane-based chemotherapy
Sipuleucel-T	Vaccine: patient's dendritic cells engineered in vitro to attack PSMA on prostate cells	Asymptomatic or minimally symptomatic patients with mCRPC without evidence of visceral disease
PARP inhibitors	Unrepaired single-strand breaks leading to double-strand breaks and DNA lethality	mCRPC, especially with *BRCA*, *BRCA2*, and *ATM* mutations

ADT, androgen deprivation therapy; AR, androgen receptor; BCL2, B-cell lymphoma/leukemia 2; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PARP, poly(ADP-ribose) polymerase; PSMA, prostate-specific membrane antigen.

remains to be determined. Additionally, the effect on OS is still being investigated, given early immature data. Furthermore, additional studies, including the TALAPRO-3 (NCT04821622) and AMPLITUDE (NCT04497844) trials, are testing the utility of PARP inhibition in selected patients with mHSPC. These studies will be critically important for defining the disease context for PARP inhibition in selected and unselected patients with advanced prostate cancer.

The Use of Precision Medicine Strategies

As approved therapeutic agents are being allocated to relatively unselected patients depending on their clinical characteristics, there remains a need for optimal sequencing and combinations of novel and older drugs, as well as reliable biomarkers to predict response to therapy, thus facilitating the correct match between the patient and a suitable treatment regimen.[82-84] Several landmark studies in patients with advanced prostate cancer, especially CRPC, have unraveled the genomic alterations frequently observed in advanced prostate cancer states. Robinson and colleagues reported that a vast majority of patients with mCRPC showed a clinically targetable somatic or germline mutation.[85] They highlighted the somatic mutations in *BRCA1/2*, *ATM*, the PI3K pathway, the DNA repair pathway, RAF kinases, cyclin-dependent kinase (CDK) inhibitors, and the WNT pathway. Pritchard and colleagues demonstrated that nearly 12% of patients with advanced prostate cancer have germline alterations in DNA repair genes.[86] Other studies have also found somatic and germline mutations in advanced prostate cancer, including *TP53*, *PIK3CA*, *BRCA1/2*, *PTEN*, *APC*, *CDK12*, and *ATM*.[87-92] Together, these studies have led to a renaissance of studies with targeted agents in advanced prostate cancer.

Genomic testing is frequently performed in patients with mCRPC, often to identify actionable therapy targets such as HRR mutations. Genetic testing for multiple genes is becoming more prevalent and is essential to identifying patients with mCRPC who are eligible for precision medicine.[93] With future trials becoming more biomarker-driven, this will most certainly cause a shift in the treatment landscape of advanced disease. Some ways to optimize precision medicine would be to facilitate access to genomic testing in diverse populations, increase awareness among providers, and hire more genetic counselors.[93,94]

Future Trials

Multiple novel agents and combination therapies are currently in clinical testing. This includes: (1) targeted therapies such as CDK4/6 inhibitors, AKT inhibitors, and others; (2) radioligand treatments such as ^{225}Ac-PSMA-617 and other radioligands to targets such as delta-like ligand 3 (DLL3); (3) AR-targeting agents such as ARV-110, a chimeric protein that promotes the ubiquitination and

degradation of the androgen receptor; and (4) immunotherapies including bispecific antibodies and chimeric antigen receptor T-cell therapies (NCT02975934, NCT04493853, NCT03072238, NCT03888612).[95-97] Although the volume of ongoing trials is high, there is also an unmet need to better understand the patient selection of therapy and the optimal treatment sequence.

Along with therapeutics, there have been advances in prostate cancer imaging. The emergence of advanced positron emission tomography (PET) imaging, primarily with PSMA, will likely redefine our classifications of metastatic disease.[98,99] PSMA PET/computed tomography (CT) is a new imaging modality used to scan the whole body for prostate cancer.[98] A recent meta-analysis that included 37 studies demonstrated a sensitivity of 77% and a specificity of 95% with PSMA PET/CT.[99]

Access to new systemic therapies for genitourinary tumors remains a significant challenge in low- and middle-income countries. To improve access, a comprehensive approach is required that involves not only ensuring drug availability but also organizing public health care systems, prioritizing discussion and strategies to decrease treatment costs through rational treatment decisions, and individualized use of systemic therapies. Furthermore, there is an urgent need for more real-world data from low- and middle-income countries, and strategies to decrease drug costs must be developed. Increasing the portfolio of modern clinical trials in low- and middle-income countries is an effective and affordable way to enable cancer patients to access targeted therapies and immunotherapy.[100]

Although patient survival is improving, treatment-emergent neuroendocrine small cell carcinoma of the prostate (t-SCNC) has been recently observed with increased frequency. This is a particularly aggressive form of prostate cancer that is often responsible for the development of androgen resistance in CRPC.[101] Studies show that patients with t-SCNC have particularly aggressive disease that is insensitive to hormonal-based treatment strategies.[99] Currently, t-SCNC is largely treated with platinum-based chemotherapy.[102] The addition of programmed death ligand 1 inhibitors to chemotherapy is under investigation.[103] Alisertib, a new agent that inhibits the interaction between N-myc and Aurora kinase A, failed to meet the primary endpoint, but exceptional responders were identified in the trial. Responders were found to have N-myc overactivity, suggesting that a subset of patients with t-SCNC may benefit from it.[104] Rovalpituzumab, which targets delta-like ligand 3 expressed explicitly in neuroendocrine tumors, also failed to show an adequate response rate in phase 1 and 2 trials. Despite that, DLL3 remains a promising therapeutic target, with novel DLL3-targeting antibody-drug conjugates under development.

Conclusion

In the past decade, newer therapeutics have changed the metastatic prostate cancer treatment paradigm. In addition, advanced imaging will affect how we define metastatic prostate cancer. Along with ADT, chemotherapy and ARSIs have demonstrated a significant survival benefit for HSPC patients. Additionally, as treatments populate the mHSPC setting, more questions about the optimal therapy sequence will emerge. Genomic sequencing has revolutionized personalized medicine, especially for the treatment of patients with CRPC. Newer trials focusing on combination therapies for CRPC have demonstrated significant improvements in survival. At the same time, as more effective treatments are established, older treatments without objective measures of benefit (PSA response, objective response, or PFS prolongation) will become used less often. Current and future trials will help us evolve and standardize the treatment regimen for localized and metastatic prostate cancer.

Disclosures

Drs Jani, Abdallah, Mouchati, and Herchenhorn do not have any disclosures. Dr McKay has served as a consultant or advisor to Aveo, Astellas, Medivation, AstraZeneca, Bayer, Bristol Myers Squibb, Calithera Biosciences, Caris, Dendreon, Exelixis, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Tempus, and Vividion Therapeutics.

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