Contemporary Management of Advanced Prostate Cancer: An Evolving Landscape

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Abstract: Recent population-based studies suggest that the incidence of advanced and metastatic prostate cancer may be increasing. Concurrently with this apparent stage migration toward advanced disease, several major developments have occurred in the treatment paradigm for men with advanced prostate cancer. These include the US Food and Drug Administration approval of 8 novel agents over the last decade. In addition to novel pharmaceuticals, rapidly evolving diagnostic tools have emerged. This review provides a primer for clinicians who treat men with advanced prostate cancer, including medical oncologists, radiation oncologists, and urologists.

Keywords
Advanced prostate cancer, anti-androgen, castration-resistant, castration-sensitive, prostate cancer, prostate-specific membrane antigen

Introduction

Prostate cancer is the most common solid-organ malignancy among men in the United States.[1] In the years following the recommendation of the U.S. Preventive Services Task Force against prostate-specific antigen (PSA) screening, rates of prostate cancer screening and biopsy detection declined.[2-4] However, in recent years, population-based evidence suggests that the incidence of advanced and metastatic prostate cancer is rising.[4-6] Concurrently with the ongoing stage migration toward advanced disease, a dramatic transformation has occurred in the treatment landscape for men with advanced and metastatic prostate cancer. The US Food and Drug Administration (FDA) has approved 8 novel agents since 2010 to treat advanced prostate cancer. Beyond drug therapy, interest is also increasing in novel diagnostic tools, as well as in potential roles for local therapy among patients with advanced disease. This review serves as a primer for urologists, medical oncologists, and radiation oncologists to navigate the rapidly evolving landscape of advanced prostate cancer.

Metastatic Castration-Resistant Prostate Cancer

The transformation of the treatment of advanced prostate cancer during the last decade began among patients with metastatic castration-resistant prostate cancer (M1 CRPC). These are patients who have radiographic evidence of metastatic disease and rising PSA levels despite appropriate androgen deprivation therapy (ADT), with androgen levels in the castration range. Historically, men with

M1 CRPC were offered only palliative treatment with mitoxantrone and prednisone.[7,8] However, since the FDA approval of docetaxel in 2004 as first-line chemotherapy for M1 CRPC, numerous novel therapies have gained FDA approval. These interventions have diverse mechanisms of actions and include cytotoxic chemotherapy with cabazitaxel (Jevtana, Sanofi-Aventis), immunotherapy with sipuleucel-T (Provenge, Dendreon), radiotherapy with radium-223 (Xofigo, Bayer), androgen synthesis blockade with abiraterone, and androgen receptor (AR) signaling inhibition with enzalutamide (Xtandi, Astellas).[9-16] The appropriate indication for the use of each medication may be challenging, given the agents' unique side effect profiles, the broad health status of men who present with M1 CRPC, and the inclusion criteria of the studies that validated use of the agents. Accordingly, the American Urological Association (AUA) has stratified patients with M1 CRPC according to symptom status, performance status, and prior docetaxel chemotherapy in their guideline for the treatment of castration-resistant prostate cancer.[7]

Docetaxel

Docetaxel is a cytotoxic chemotherapeutic agent that binds to intracellular microtubules, inhibiting their disassembly and preventing the transition from metaphase to anaphase.[17] In 2004, docetaxel became the first chemotherapeutic agent with a proven survival benefit to receive FDA approval for patients with M1 CRPC, on the basis of results of the TAX 327 trial (Table 1).[8,18] In this study, 1006 patients with good performance status were randomly assigned to docetaxel at 75 mg/m^2 every 3 weeks (q3wk), docetaxel at 30 mg/m^2 weekly, or mitoxantrone at 12 mg/m^2 weekly.[18] Median overall survival (OS) was 18.9 months in the docetaxel q3wk arm vs 16.5 months in the mitoxantrone arm (hazard ratio [HR] for docetaxel, 0.75; P<.01). In the SWOG 9916 trial, docetaxel/estramustine (Emcyt, Pfizer) was compared with mitoxantrone/prednisone for 12 cycles in 674 in men with M1 CRPC. Patients in the docetaxel arm vs those in the mitoxantrone arm had a 20% reduction in risk for death and a median OS of 17.5 vs 15.6 months, respectively (P=.02).[19] Given these outcomes, the AUA recommends docetaxel as a treatment option in nearly all patients with M1 CRPC, including those with good performance status who have previously received docetaxel but were forced to discontinue owing to side effects. Per the AUA, docetaxel is contraindicated in men with poor performance status or those whose disease has progressed despite prior docetaxel therapy.

Abiraterone

Abiraterone is an oral medication that inhibits the cytochrome P450 17A1 (CYP17A1) enzyme in the adrenal cortex. This enzyme is required for the production of dehydroepiandrostenedione (DHEA), which is ultimately converted to testosterone in the testis. CYP17A1 is also present in testicular and prostatic tissue.[20] Abiraterone is administered concomitantly with prednisone to counteract the decreased cortisol production caused by CYP17A1 inhibition.

After initially being approved by the FDA in 2011 for the treatment of patients with M1 CRPC whose disease progressed after docetaxel, the indication for abiraterone was expanded in 2012 to include all patients with M1 CRPC, regardless of performance status or prior docetaxel. In the COU-AA-302 study, 1088 men with M1 CRPC who had not received prior chemotherapy were randomly assigned to prednisone at 5 mg twice daily plus either abiraterone at 1000 mg daily or placebo.[14,15] In the interim analysis, patients in the abiraterone arm demonstrated an improvement in radiographic progression-free survival (PFS) compared with those in the placebo arm (HR, 0.43; P<0.1), and the final analysis showed an improvement in median OS (34.7 vs 30.3 months, respectively; HR, 0.81; P<.01).[14,15] In the COU-AA-301 study, 1195 patients who had received prior docetaxel chemotherapy were randomly assigned to prednisone at 5 mg twice daily plus either abiraterone at 1000 mg (797 patients) or placebo (398 patients).[13] Median OS was longer in the abiraterone group than in the placebo group (14.8 vs 10.9 months, respectively; HR, 0.65; P<.001). Treatment-associated side effects, which were primarily related to excess mineralocorticoids due to CYP17A1 inhibition, included hypokalemia, hypertension, and fluid retention.[13,15] Liver function test abnormalities were also more common with abiraterone than with placebo.

Enzalutamide

First-generation anti-androgens, such as bicalutamide, flutamide, and nilutamide, exert their antitumoral activity via competitive inhibition of the AR. Enzalutamide provides a more comprehensive blockade, via multifocal signaling inhibition of the AR.[21] This is conventionally thought to occur in 3 ways: (1) competitive binding of the AR, similar to first-generation anti-androgens; (2) prevention of nuclear translocation of the AR; and (3) inhibition of interaction of the hormone/AR complex with DNA.[21]

Like abiraterone, enzalutamide can now be used in all patients with M1 CRPC, regardless of their performance status or chemotherapy history. However, it was first approved by the FDA in 2012 for patients with M1 CRPC who had previously received docetaxel, and the indication was subsequently expanded in 2014 to include all patients with M1 CRPC. In the PREVAIL study, 1717 treatment-naive patients were randomly assigned to either enzalutamide at 160 mg daily or placebo.[16] Patients in the enzalutamide arm had a 29% decrease in risk for death (72% of the enzalutamide patients and 63% of

Table 1. Major Clinical Trials Involving the Various Therapies Used to Treat Advanced Prostate Cancer

Drug	Study	Phase	No. of Patients	Primary Endpoint	Result
M1 CRPC					
Docetaxel vs mitoxantrone	TAX 327	3	1006	OS	HR=0.75, *P*<.01
Docetaxel vs mitoxantrone	SWOG 9916	3	674	OS	17.5 vs 15.6 mo, HR=0.80, *P*=.02
Abiraterone vs placebo	COU-AA-302	3	1088	OS	34.7 vs 30.3 mo, HR=0.81, *P*<.01
Abiraterone vs placebo	COU-AA-301	3	1195	OS	14.8 vs 10.9 mo, HR=0.65, *P*<.001
Enzalutamide vs placebo	PREVAIL	3	1717	OS, PFS	72% vs 63% alive at data cutoff, HR=0.71, *P*<.001; 65% vs 14% 12-mo PFS, HR=0.19, *P*<.001
Enzalutamide vs placebo	AFFIRM	3	1199	OS	18.4 vs 13.6 mo, HR=0.63, *P*<.001
Sipuleucel-T vs placebo	IMPACT	3	512	OS	25.8 vs 21.7 mo, HR=0.78 , *P*=.03
Radium-223 vs placebo	ALSYMPCA	3	921	OS	14.9 vs 11.3 mo, HR=0.70, *P*<.001
Cabazitaxel vs mitoxantrone	TROPIC	3	755	OS	15.1 vs 12.7 mo, HR=0.70, *P*<.001
Cabazitaxel vs abiraterone or enzalutamide	CARD	3	255	PFS	8.0 vs 3.7 mo, HR=0.54, *P*<.001
Cabazitaxel/carboplatin vs cabazitaxel	–	2	160	PFS	7.3 vs 4.5 mo, HR=0.69, *P*=.018
M1 CSPC					
ADT/docetaxel vs ADT	CHAARTED	3	790	OS	57.6 vs 44.0 mo, HR=0.61, *P*<.001
ADT vs ADT/zoledronic acid vs ADT/docetaxel vs ADT/zoledronic acid/docetaxel	STAMPEDE	3	2962	OS	71 mo vs NA (HR=0.94, *P*=.450) vs 81 mo (HR=0.78, *P*=.006) vs 76 mo (HR=0.82, *P*=.022)
ADT/abiraterone vs ADT	STAMPEDE	3	1917	OS	83% vs 76%, HR=0.63, *P*<.001
ADT/enzalutamide vs ADT	ARCHES	3	1150	PFS	34.9% vs 15.9%, HR=0.39, *P*<.001
ADT/enzalutamide vs ADT	ENZAMET	3	1125	OS	HR=0.67, *P*=.002
Apalutamide/ADT vs ADT	TITAN	3	1052	PFS, OS	68.2% vs 47.5%, HR=0.48, *P*<.001; 82.4% vs 73.5%, HR=0.67, *P*=.005
M0 CRPC					
Apalutamide/ADT vs placebo/ADT	SPARTAN	3	1207	OS	73.9 vs 59.9 mo, HR=0.78, *P*=.016
Enzalutamide vs placebo	PROSPER	3	1401	OS	67.0 vs 56.3 mo, HR=0.73, *P*=.001
Darolutamide vs placebo	ARAMIS	3	1509	3-y OS	83% vs 77%, HR=0.69, *P*=.003

ADT, androgen deprivation therapy; HR, hazard ratio; M0 CRPC, nonmetastatic castration-resistant prostate cancer; M1 CRPC, metastatic castration-resistant prostate cancer; M1 CSPC, metastatic castration-sensitive prostate cancer; mo, month(s); NA, not available; OS, overall survival; PFS, progression-free survival; y, year.

the placebo patients were alive at the time of data cutoff; *P*<.001). They also demonstrated improvements in all secondary endpoints, including time to initiation of chemotherapy, time to first skeletal event, any soft-tissue response, and time to PSA progression. In the AFFIRM trial, 1199 patients with M1 CRPC who had previously received docetaxel were randomized in a 2:1 ratio to either enzalutamide at 160 mg (n=899) or placebo (n=300). Median OS was longer in the enzalutamide arm than in the placebo arm (18.4 vs 13.6 months, respectively; HR for death, 0.63; *P*<.001).[22] Notably, 5 patients in the enzalutamide arm in AFFIRM had seizures,[22] and the potential for central nervous system toxicity must be considered before enzalutamide is started.

Sipuleucel-T

In April of 2010, sipuleucel-T became the first active cellular immunotherapy approved by the FDA, although it is approved for use in only patients with M1 CRPC who are asymptomatic or minimally symptomatic. It is often referred to as a cancer "vaccine." After a leukapheresis session, autologous antigen-presenting cells are activated ex vivo against a

recombinant fusion protein consisting of a prostate antigen, prostatic acid phosphatase, and granulocyte-macrophage colony–stimulating factor.[10] These activated cells are then readministered intravenously.

In the IMPACT trial, 512 men were randomly assigned in a 2:1 ratio to receive either sipuleucel-T (n=341) or placebo (n=171).[10] The placebo formulation consisted of antigen-presenting cells incubated in the absence of the recombinant fusion protein. Patients in the sipuleucel-T group had a 22% decrease in risk for death compared with those in the placebo group (*P*=.03), which translated to a 4.1-month benefit in median OS (25.8 vs 21.7 months, respectively). Notable exclusion criteria in this trial were Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scores of 2 or greater, visceral metastasis, and the administration of chemotherapy within the preceding 3 months. Chills, fever, and headache occurred more frequently in the sipuleucel-T group.

A more recent analysis of the PROCEED study provides contemporary data from a prospectively maintained database of patients with M1 CRPC treated with sipuleucel-T.[23] From 2011 to 2017, a total of 1902 patients with M1 CRPC were treated with sipuleucel-T (median follow-up, 46.6 months). The median OS was 30.7 months (95% CI, 28.6-32.2), with 964 (50.7%) patients dying of prostate cancer. The overall safety and tolerability of sipuleucel-T were acceptable; the overall incidence of serious adverse events related to sipuleucel-T was 3.9%; cerebrovascular events were the most common, occurring in 2.8% of patients.

Several studies have demonstrated the varying efficacy of sipuleucel-T among different subpopulations. In a study comparing the outcomes between White and Black men with M1 CRPC who received sipuleucel-T, Sartor and colleagues found that OS was longer in Black men than in White men (HR, 0.8; 95% CI, 0.68-0.097; *P*=.03), with a median OS of 35.3 months in Blacks and 25.8 months in Whites.[24] In addition, several studies have demonstrated a correlation between PSA levels and the treatment effect of sipuleucel-T.[25,26] A recent study by Higano and colleagues demonstrated that patients in the lowest PSA quartile of the PROCEED study had the longest time to intervention after receiving treatment with sipuleucel-T.[26]

Radium-223

The alpha-particle radiation emitted from molecules of radium-223 causes localized cytotoxic effects by inducing double-stranded DNA breaks. Given that radium-223 is a bone-seeking calcium analogue, it is targeted to areas of high bone turnover within the context of osteoblastic metastases. This localization, in conjunction with the short path traveled by the alpha particles (<100 μm), limits damage to surrounding healthy tissue.[12]

Radium-223 received FDA approval in 2013 for the treatment of symptomatic bony metastasis in M1 CRPC in the absence of visceral metastasis on the basis of the results of the ALSYMPCA trial.[11,12] After stratification based on alkaline phosphate levels, bisphosphonate use, and previous docetaxel therapy, 921 patients were randomized in a 2:1 ratio to receive 6 injections of radium-223 (n=614) or placebo (n=307). Median OS was longer in the radium-223 group than in the placebo group (14.9 vs 11.3 months, respectively; HR, 0.70; *P*<.001). This survival benefit was observed regardless of docetaxel use. Although the trial enrolled patients with ECOG-PS scores up to 2, the survival benefit was noted only in those ranked 0 or 1. However, the AUA guidelines for CRPC still recommend use of radium-223 in patients with poor performance status if the status is attributable primarily to symptoms of bony metastasis.[7]

Cabazitaxel

Cabazitaxel, which like docetaxel is a semisynthetic taxane chemotherapeutic agent, functions in a mechanistically similar fashion.[27] It garnered FDA approval in June of 2010 for use in patients with M1 CRPC who have previously received docetaxel. In the TROPIC study, 755 patients with M1 CRPC who had previously received docetaxel therapy were randomly assigned to receive prednisone at 10 mg daily plus either cabazitaxel or mitoxantrone.[9] At the final analysis, median OS was longer in the cabazitaxel group (15.1 vs 12.7 months; HR for death, 0.70; *P*<.001). The majority (82%) of patients in the cabazitaxel group had grade 3 or 4 neutropenia, and 5% of the cohort died because of this adverse event. Therefore, the FDA approval recommends neutrophil growth factor support when cabazitaxel is administered. Given the more tolerable side effect profiles of abiraterone and enzalutamide, and the cumulative toxicity of multiple courses of different chemotherapies, cabazitaxel is less favored for use in this patient population.

Recently, de Wit and colleagues published results from the CARD trial, in which 255 men with M1 CRPC were randomly assigned to receive either cabazitaxel or an inhibitor of androgen signaling (abiraterone or enzalutamide).[28] Inclusion criteria were disease progression within the past 12 months after having received previous docetaxel plus either abiraterone or enzalutamide. When the primary outcome (radiographic PFS) was analyzed, cabazitaxel outperformed alternative anti-androgen therapy, with median PFS longer in the cabazitaxel arm (8.0 months) than in the alternative arm (3.7 months; HR, 0.54; 95% CI, 0.40-0.73; *P*<.001). In addition, OS data suggested a benefit for patients who received cabazitaxel vs alternative anti-androgen therapy (HR, 0.64; 75% CI, 0.46-0.89; *P*=.0078; median OS, 13.6 vs 11.0 months, respectively).

Cabazitaxel can also be used in combination with carboplatin for the treatment of M1 CRPC. A recent phase 1/2 trial suggested that PFS was significantly longer in patients who received combination therapy (7.3 months) than in those treated with cabazitaxel alone (4.5 months; HR, 0.69 [95% CI, 0.50-0.95]; *P*=.018).[29] Although more adverse events occurred in the combination arm (20% vs 9%), the investigators concluded that the treatment was safe and well tolerated.

Theranostics

An emerging frontier in the treatment of M1 CRPC is theranostics, in which novel diagnostics are combined with targeted therapeutic agents to optimize the selection of patients for treatment and assess the treatment response. Prostate-specific membrane antigen (PSMA) serves as the foundation for theranostics in patients with M1 CRPC whose disease has progressed after treatment with abiraterone, enzalutamide, and taxane chemotherapy. Positron emission tomography/computed tomography (PET/CT) imaging with gallium 68 PSMA-11, which binds to PSMA in cancer cells, is used to determine baseline PSMA activity, and a beta particle–emitting radiotherapeutic PSMA ligand, lutetium 177 PSMA-617, serves as treatment in those with a high level of PSMA expression. Treatment response is followed with additional ^{68}Ga-PSMA-11 PET/CT. In results from the single-arm, phase 2 LuPSMA trial, Hofman and colleagues reported that a PSA decline of 50% or more occurred in 17 of 30 patients (57%) after they were treated with ^{177}Lu-PSMA-617.[30] The most common side effects of treatment were dry mouth in 26 of 30 patients (87%), nausea in 15 (50%), and fatigue in 15 (50%). Most notably, thrombocytopenia occurred in only 4 patients (13%), highlighting the low toxicity profile of ^{177}Lu-PSMA-617. In the ongoing TheraP trial, Hofman and colleagues are comparing ^{177}Lu-PSMA-617 with cabazitaxel for the treatment of M1 CRPC.[31] Initial results have demonstrated that a reduction in PSA of at least 50% occurred in a greater proportion of patients treated with^{177}Lu-PSMA-617 than of those treated with cabazitaxel (66% vs 37%, respectively; *P*<.001). With regard to toxicity, grade 3 or 4 adverse events were more common in the cabazitaxel arm than in the ^{177}Lu-PSMA arm (54% vs 35%).

Several other studies have also evaluated the efficacy of ^{177}Lu-PSMA in treating M1 CRPC. In a recent prospective, phase 2 trial of ^{177}Lu-PSMA therapy in 14 men with disease progression after anti-androgen (abiraterone and/or enzalutamide) and taxane treatment and with detectable ^{68}Ga-PSMA uptake on PET/CT,[32] a PSA reduction (mean reduction, 59%) occurred in 10 patients, and standardized uptake values of ^{68}Ga-PSMA at PET/CT screening were predictive of a PSA reduction of greater than 30%.[32] This finding is being further evaluated in the VISION study (NCT03511664), a prospective, multicenter, phase 3 randomized control trial that aims to enroll a cohort of 750 men with similar prior treatment histories and positive results on ^{68}Ga-PSMA PET/CT to either 6 cycles of ^{177}Lu-PSMA or placebo.[33] The estimated study completion date is December 2021. Trials involving alpha particle–emitting radiotherapeutic PSMA ligands, such as actinium and thorium, are also in progress.

Metastatic Castration-Sensitive Prostate Cancer

The second realm of advanced prostate cancer management to undergo a paradigm shift was the treatment of patients with metastatic castration-sensitive (also referred to as castration-naive or hormone-sensitive) prostate cancer (M1 CSPC). A patient with M1 CSPC is one who is not on ADT and who has eugonadal androgen levels at the time metastatic disease is diagnosed.[34,35] Before 2004, no treatments for advanced prostate cancer aside from ADT were available that provided survival benefit. Over the course of the following decade, several treatments for M1 CRPC were reported, and more recently, the use of many of these drugs has extended into the castration-sensitive space.

The first major breakthrough in the treatment of M1 CSPC was the CHAARTED trial.[36] This study randomly assigned 790 patients with M1 CSPC to receive ADT alone or ADT plus docetaxel. Median OS was longer in the ADT-plus-docetaxel arm than in the ADT-alone arm, at 57.6 vs 44.0 months, respectively (*P*<.001). Stratifying the patients on the basis of volume of disease (high volume defined as the presence of visceral metastases or >4 bone lesions with >1 lesion beyond the vertebral bodies and pelvis) revealed a particular benefit of docetaxel among patients with high-volume disease. On secondary analysis, median time to castration resistance (20.2 vs 11.7 months) and median time to clinical progression (33.0 vs 19.8 months) also favored the docetaxel arm (*P*<.001). Lastly, 86% of patients in the docetaxel arm completed all 6 cycles.[36]

The STAMPEDE trial also evaluated docetaxel in men with M1 CSPC. The 4 treatment arms were as follows: ADT, ADT plus zoledronic acid (a bisphosphonate that has been shown to reduce skeleton-related events in M1 CRPC11), ADT plus docetaxel, and ADT plus zoledronic acid and docetaxel. This trial included 2962 men with local recurrence or metastasis randomized in a 2:1:1:1 ratio. Overall, only the treatments that included docetaxel showed survival advantages compared with ADT alone. Results for the overall cohort are displayed in Table 1. On subgroup analyses of the patients with metastases (n=1817), survival improvements were noted only in those receiving docetaxel; median survival was 45 months

with ADT alone vs 60 months with ADT plus docetaxel (HR, 0.76; *P*=.005) vs 46 months with ADT plus zoledronic acid (HR, 0.93; *P*=0.42) vs 55 months with ADT plus docetaxel and zoledronic acid (HR, 0.79; *P*=.015). In patients with no evidence of metastases, docetaxel was not associated with a survival advantage compared with ADT alone. Of the patients in the arm that received ADT plus docetaxel and the arm that received ADT plus zoledronic acid and docetaxel, 77% and 71%, respectively, completed all 6 cycles. On the basis of the results of CHAARTED and STAMPEDE, docetaxel was recommended as the standard of care for M1 CSPC.[36,37]

Despite the noted benefits of docetaxel, the side effect profile is not insignificant; similarly, other barriers to its use include advanced age, poor performance status, coexisting illnesses, and patient preferences. As a result, the LATITUDE trial was implemented to test abiraterone plus prednisone in the M1 CSPC setting.[38] A total of 1199 patients were randomly assigned to ADT plus abiraterone vs ADT plus placebo. The 3-year OS was improved in the abiraterone group vs the placebo group (66% vs 49%, respectively; HR, 0.62; *P*<.001), and the median radiographic PFS also was significantly improved (33 vs 14.8 months, respectively; HR, 0.47; *P*<.001). All secondary endpoints, including median times to pain progression, chemotherapy, or any prostate cancer therapy, were significantly improved in the abiraterone arm.[38]

In a second study of abiraterone in M1 CSPC, also from the STAMPEDE trial, abiraterone was tested as a first-line treatment for high-risk, locally advanced disease or M1 CSPC, or for disease previously treated with radical surgery or radiotherapy and relapsing with high-risk features. A total of 1917 patients were randomly assigned to ADT alone or ADT plus abiraterone. The 3-year OS was 83% in the group that received ADT plus abiraterone and 76% in the ADT-alone group (HR, 0.63; *P*<.001). A preplanned analysis of 1002 patients with M1 CSPC also showed improved OS in the abiraterone group (HR, 0.61). Similar benefits were seen for 3-year failure-free survival.[39]

In addition to docetaxel and abiraterone, the ARCHES and the ENZAMET trials both investigated the use of enzalutamide in M1 CSPC.[35,40] In the ARCHES trial, 1150 patients were randomly assigned to ADT plus placebo or ADT plus enzalutamide.[35] Radiographic PFS, the primary endpoint, was 34.9% in the ADT-plus-enzalutamide arm and 15.9% in the ADT-alone arm, with a risk reduction of 61% (HR, 0.39; *P*<.001). Median PFS was not reached in the ADT-plus-enzalutamide arm and was 19.0 months in the ADT-plus-placebo arm. These significant findings were noted in all subgroups, regardless of volume of disease or prior docetaxel use. Similarly, the time to PSA progression, time to initiation of new antineoplastic therapy, objective response rate, and risk for castration resistance were all improved in the enzalutamide arm. The OS data were immature; median duration was not met for either group.[35]

In the ENZAMET trial, 1125 patients were randomly assigned to treatment with either ADT plus enzalutamide or ADT alone.[40] OS, the primary endpoint, was significantly improved in the enzalutamide arm (HR, 0.67; *P*=.002), although the median survival time was not yet determinable in either arm. Secondary endpoints, specifically PSA (HR, 0.39; *P*<.001) and clinical PFS (HR, 0.40; *P*<.001), both favored the enzalutamide arm. On the basis of both the ENZAMET and ARCHES trials, enzalutamide is now considered a viable treatment option in M1 CSPC.[35,40]

At the same time that the enzalutamide trials were reported, the TITAN trial was published, which investigated the use of apalutamide (Erleada, Janssen) in M1 CSPC. In this study, 1052 patients were randomly assigned to apalutamide plus ADT or placebo plus ADT. The 2 primary endpoints were radiographic PFS and OS. Radiographic PFS at 24 months was 68.2% in the apalutamide arm and 47.5% in the placebo arm (HR, 0.48; *P*<.001). OS at 24 months was 82.4% in the apalutamide arm and 73.5% in the placebo arm (HR, 0.67; *P*=.005). In subgroup analyses, apalutamide provided benefit for both endpoints in high-volume disease, but OS was not significantly improved in low-volume disease. Additionally, the benefit of apalutamide was blunted on both endpoints in patients who had previously received docetaxel.

On the basis of these landmark studies, docetaxel, abiraterone, enzalutamide, and apalutamide are all FDA-approved to treat M1 CSPC. Still, without direct head-to-head data comparing these treatments with one another, optimal treatment selection is yet to be defined and remains a decision tailored to each individual patient.[41]

Nonmetastatic Castration-Resistant Prostate Cancer

ADT may lead to the development of CRPC without any detection of metastatic disease on conventional imaging (ie, negative results on bone scan and computed tomography of the chest/abdomen/pelvis). Patients who have nonmetastatic castration-resistant prostate cancer (M0 CRPC) historically have been managed with watchful waiting until metastatic disease is detected.[7] Metastatic disease has been reported among men who have M0 CRPC within the first 3 years, and bone metastases have developed in one-third within 2 years after the diagnosis.[42] Thus, these men are considered to have active prostate cancer, a disease state that is ripe for management with novel therapeutic strategies.

In CRPC, the AR pathway remains activated and

therefore represents a potential therapeutic target.[7,43] Three distinct second-generation AR inhibitors—apalutamide, enzalutamide, and darolutamide (Nubeqa, Bayer)—have all gained FDA approval for the treatment of M0 CRPC. The AUA guidelines on advanced prostate cancer suggest that patients with M0 CRPC should be treated with continuous ADT plus either apalutamide or enzalutamide. (Note: darolutamide had not yet been approved at the time of guideline publication.)

The SPARTAN trial, published in early 2018,[44] randomly assigned 1207 men with M0 CRPC and a PSA doubling time of less than 10 months in a 2:1 ratio to apalutamide/ADT or placebo/ADT. Median metastasis-free survival was 40.5 months for apalutamide/ADT, which was 24.3 months longer than that for placebo/ADT (HR, 0.28; *P*<.001). The trial reported a 72% reduction in risk for distant metastases or death. Notable secondary endpoints all favored apalutamide over placebo, including symptomatic progression (HR, 0.45; *P*<.001), time to metastasis (HR, 0.29; *P*<.001), and median PFS (HR, 0.29; *P*<.0001). Median PFS in the apalutamide group was 25.8 months longer. In a recent follow-up publication, the investigators reported better OS in the apalutamide group than in the control group (median, 73.9 vs 59.9 months; *P*=.016).[45] A concern regarding the design of this study was the inclusion of men with lymphadenopathy of less than 2 cm (N1 disease), who accounted for 16% of the recruited population; however, the benefits of apalutamide were noted in all subgroups (including the men with N1 disease). Adverse events caused by apalutamide included fatigue, hypertension, rash, diarrhea, nausea, weight loss, falls, and seizures. Particular attention was given to hypothyroidism (8.1% with apalutamide vs 2% with placebo), with subsequent AUA guideline recommendations to monitor patients' thyroid function during apalutamide treatment.[7] The treatment effect was consistently favorable, and when the trial was unblinded in 2017, all patients from the placebo arm were offered apalutamide.

Similar to SPARTAN, the PROSPER trial evaluated enzalutamide in a randomized, double-blind, placebo-controlled study with 1401 patients.[46] Men included in this study had M0 CRPC with a PSA doubling time of less than 10 months and remained on ADT; they were randomized in a 2:1 ratio to enzalutamide or placebo. Median metastasis-free survival was 22 months longer in the enzalutamide group (36.6 months vs 14.7 months for placebo). Median time to PSA progression was 33 months longer in the enzalutamide group, with a 93% reduction in relative risk for PSA progression favoring the enzalutamide cohort. Enzalutamide was also associated with a longer time to subsequent antineoplastic therapy (39.6 months vs 17.7 months for placebo; *P*<.001). In a recent follow-up publication, the authors reported improved OS in the enzalutamide group compared with the control group (median, 67.0 vs 56.3 months; *P*=.001).[47]

Most recently, the introduction of darolutamide via the ARAMIS trial has added a third agent to the treatments for patients with M0 CRPC. ARAMIS randomly assigned 955 men to darolutamide and 554 men to placebo.[48] Median metastasis-free survival was 40.4 months in the darolutamide group vs 18.4 months in the placebo group (HR, 0.41; *P*<.001). Benefits were consistent across all subgroups. In a recent follow-up publication, the investigators reported improved OS in the darolutamide group at 3 years (83% vs 77%).[49] Notably, an adverse event rate below 10% was reported—the lowest among all 3 agents. Unlike enzalutamide and abiraterone, darolutamide did not have a higher rate of fractures, falls, seizures, or hypertension than placebo. Although the side effect profile appeared to favor darolutamide, direct head-to-head comparative studies are needed to guide treatment decisions for men with M0 CRPC. Quality-of-life outcomes would also be of tremendous value in the shared decision-making process.

Novel imaging, such as PSMA positron emission tomography (PET), may offer better sensitivity in detecting prostate cancer than conventional imaging and could potentially improve patient risk stratification.[50] Fendler and colleagues used PSMA PET to assess 200 patients with high-risk M0 CRPC and found that 55% did in fact have distant metastases.[51] Thus, as advanced imaging modalities continue to increase the diagnostic sensitivity for metastatic disease, the number of patients with true M0 CRPC may actually decrease.

Novel Therapies in Metastatic Castration-Resistant Prostate Cancer

Recently, significant interest has been shown in moving beyond androgen-based therapeutics into the realm of molecularly guided therapies for advanced prostate cancer. The poly(ADP-ribose) polymerase (PARP) inhibitors represent one class of molecularly guided therapies used to treat patients with a mutation in genes involved in homologous recombination repair. PARP inhibitors work by inhibiting the activity of catalytic PARP enzymes, thereby trapping PARP on DNA sites and inhibiting DNA repair. Cells with defective recombination repair are susceptible to PARP inhibition, which results in genetic instability and ultimately cell death.[52] To date, olaparib (Lynparza, AstraZeneca) and rucaparib (Rubraca, Clovis Oncology) are the only 2 PARP inhibitors with FDA approval in advanced prostate cancer. In published results from the PROfound trial, de Bono and colleagues reported that patients in the olaparib group had a significantly longer PFS, defined as lack of radiographic progression, when compared with the control group (median, 7.4 vs 3.6

Table 2. Novel Molecularly Guided Therapies Under Investigation for the Treatment of Advanced Prostate Cancer

Drug	Study	Phase	Primary Endpoint	Result	FDA Approval Status
Olaparib	PROfound	3	OS	19.1 vs 14.7 mo, HR=0.69, *P*=.02	Approved
Rucaparib	TRITON2	2	PSA/radiographic response	43.90%	Approved
Talazoparib	TALAPRO-1	2	ORR	25.60%	Not approved
Niraparib	GALAHAD2	2	ORR	41% in *BRCA1/2*-mut vs 9% in *BRCA*-wt	Breakthrough designation
Pembrolizumab	KEYNOTE-199	2	RR	5% for PD-L1–pos vs 3% for PD-L1–neg	Approved for solid tumors with MSI or MMR mut

MMR, mismatch repair gene; MSI, microsatellite instability; mut, mutated/mutation; neg, negative; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; pos, positive; PSA, prostate-specific antigen; RR, response rate; wt, wild-type.

months, respectively; *P*<.001).[53] In addition, the investigators reported an improved OS in the olaparib group compared with the control group (median, 19.1 vs 14.7 months, respectively; *P*=.02; Table 2).[54] In a subgroup analysis in which patients were stratified by specific gene alterations, those with *BRCA1* or *BRCA2* mutations were found to derive the greatest benefit from olaparib, whereas patients with the *PPP2R2A* gene actually fared worse with olaparib than with control. Regarding adverse events, the incidence of grade 3 or higher adverse events was 51% in the olaparib group vs 38% in the control group. The most common adverse event in the olaparib group was anemia (46% for all grades; 21% for grade ≥3). Study discontinuation occurred in 18% of the olaparib group vs 8% of the control group.[53] In phase 2 results from TRITON2, Abida and colleagues reported that 43.90% of the patients with a *BRCA2* mutation had a confirmed radiographic and PSA response to rucaparib.[54] The ongoing TRITON3 study is evaluating rucaparib vs physician's choice of second-line AR therapy or docetaxel in chemotherapy-naive patients with M1 CRPC (NCT02975934).

Several non–FDA-approved PARP inhibitors are also being investigated actively. In the first interim analysis of the TALAPRO-1 trial, de Bono and colleagues reported that the overall response rate of patients receiving talazoparib (Talzenna, Pfizer) was 25.6% (95% CI, 13.5%-41.2%), with a 50% response rate for patients having a *BRCA1/2* mutation.[55] In addition, PFS was longer in the patients with a *BRCA1/2* mutation than in those with an *ATM* mutation (8.2 vs 3.5 months, respectively). Niraparib (Zejula, GSK/Tesaro) is another PARP inhibitor that has been used successfully in patients with *BRCA1/2* mutations. An interim analysis from the GALAHAD trial studying niraparib in patients with M1 CRPC and *BRCA* mutations revealed an ORR of 41%, and niraparib has recently received breakthrough therapy designation from the FDA for the treatment of M1 CRPC.[56]

Drugs that target cells with microsatellite instability (MSI) represent another class of molecularly guided therapies used for the treatment of M1 CRPC. MSI is a mechanism of a dysregulated mismatch repair (MMR) system, which results in the inability of a cell to correct spontaneous somatic mutations.[57] One MSI agent with applications in advanced prostate cancer is pembrolizumab (Keytruda, Merck). In the phase 2 KEYNOTE-199 study, Antonarakis and colleagues reported that the rate of response to pembrolizumab in patients with M1 CRPC positive for programmed death ligand 1 (PD-L1) was higher than the response rate in patients with PD-L1–negative disease, at 5% (95% CI, 2%-11%) vs 3% (95% CI, <1%-11%).[58] In addition, median OS was longer in the PD-L1–positive group (9.5 vs 7.9 months). *CDK12* mutations portend a poor prognosis in advanced prostate cancer. However, unlike most patients with advanced prostate cancer, a subset of patients with *CKD12* mutations may exhibit unique sensitivity to immunotherapy, including programmed death 1 (PD-1) inhibitors and other immune checkpoint inhibitors.[59,60] Another MSI treatment under investigation is combination therapy with nivolumab (Opdivo, Bristol-Myers Squibb) plus ipilimumab (Yervoy, Bristol-Myers Squibb). In preliminary results from the phase 2 CheckMate 650 trial, Sharma and colleagues reported a median OS of 19.0 months before chemotherapy and 15.2 months after chemotherapy.[61] Several studies have demonstrated encouraging initial results with the combination of pembrolizumab and other agents, including olaparib,[62] docetaxel,[63] and enzalutamide.[64] Investigators are also studying the combination of cryotherapy and pembrolizumab.[65] The efficacy of ipilimumab plus radiation therapy to metastatic lesions is being investigated as well, with preliminary results demonstrating a significant OS benefit compared with placebo.[66] The explorations of these new combination therapies are encouraging, and we look forward to seeing the evolution of this space in coming months.

On the basis of these studies, professional societies have embraced molecularly guided therapy for patients

with advanced prostate cancer. The National Comprehensive Cancer Network (NCCN) now recommends germline testing for MSI and homologous recombination repair genes (including *BRCA1/2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*) for all patients with high-risk localized or advanced prostate cancer, a strong family history of prostate cancer, or a known family history of high-risk germline mutations.[34]

Emerging Role for Local Therapy in Metastatic Prostate Cancer

In addition to the aforementioned novel pharmaceutical agents, interest is emerging in the role of local therapy for patients with metastatic prostate cancer. The STAMPEDE Arm H trial randomized more than 2000 patients with low-volume metastatic disease to either ADT alone or ADT plus external beam radiation therapy (EBRT) to the primary tumor.[67] No difference in OS was observed, although failure-free survival (FFS) was greater among the patients receiving EBRT (HR, 0.76; *P*<.0001). A subgroup analysis stratified patients according to low- vs high-volume metastatic burden. In this subanalysis, EBRT was found to be associated with improved OS (HR, 0.68) among patients with a low-volume metastatic burden. On the basis of these results, the 2019 NCCN prostate cancer guidelines include "EBRT to the primary tumor" as an acceptable treatment strategy for patients with castration-naive, low-volume metastatic disease.[26,34]

The STAMPEDE results must be interpreted cautiously, however. The only OS benefit seen in the STAMPEDE trial was in a subgroup analysis that was not predefined at the study outset. In fact, the "Conclusion" section of the STAMPEDE manuscript states that "radiotherapy did not improve OS …" for the overall cohort. Furthermore, in HORRAD, a prospective, randomized trial that compared local therapy with ADT/EBRT vs ADT alone in 432 men with low-volume M1 disease,[68] OS did not differ between the study groups (HR, 0.90; *P*=.4). With regard to prostatectomy in patients who have M1 disease, retrospective studies suggest a possible survival advantage. However, these studies are likely to have been subject to heavy selection bias, and prospective, randomized studies are warranted. Thus, when taken together, the overall evidence for local therapy in low-volume M1 prostate cancer is mixed at best. We believe this approach should be considered investigational and should by no means represent the standard of care.

Several studies are currently underway to evaluate formally the effect of local therapy in patients with low-volume M1 prostate cancer. The ongoing G-RAMPP[69] and TRoMbone[70] studies, as well as the planned STAMPEDE Arm M study, all evaluate the role of radical prostatectomy among patients with low-volume M1 prostate cancer. The PEACE1 trial is comparing ADT with ADT plus radiotherapy in this population (NCT01957436). The SWOG1802 study allows any form of local therapy (radiation or surgery) in its assessment of local therapy among men with M1 disease (NCT03678025). We are optimistic that these ongoing studies will help bring clarity to the role of local therapy in low-volume M1 prostate cancer.

Sequencing of Advanced Agents

With all the new therapies now available for the treatment of advanced prostate cancer, the question remains as to which sequence produces the best outcomes. In a retrospective study analyzing the appropriate second-line treatment for M1 CRPC, Andrews and colleagues found that patients who received docetaxel followed by second-generation ADT had a longer 3-year OS compared with patients who received ADT followed by docetaxel (82.4% vs 60.8%; *P*=.01).[71] To determine the appropriate third-line therapy for M1 CRPC, Caffo and colleagues analyzed data from 1099 patients with M1 CRPC who received treatment with at least 2 new agents after failing treatment with docetaxel.[72] The investigators found that the median OS from the start of second-line treatment was similar regardless of treatment sequence, but that the median OS from the start of third-line treatment was significantly longer among patients treated with cabazitaxel than among patients treated with abiraterone or enzalutamide (median OS, 12.2 vs 9.1 months; *P*=.039). Another study, by Khalaf and colleagues, aimed to determine the optimal sequence for the administration of enzalutamide and abiraterone plus prednisone for the treatment of M1 CRPC.[73] In this phase 2, open-label crossover trial, patients were randomly assigned to receive either abiraterone plus prednisone until evidence of PSA progression followed by crossover to enzalutamide (group A), or the opposite sequence (group B). The investigators found that time to PSA progression was longer in group A than in group B, at a median of 19.3 months (95% CI, 16.0-30.5) vs 15.2 months (95% CI, 11.9-19.8), respectively (HR, 0.66; 95% CI, 0.45-0.97; *P*=.036). In addition, a PSA response was seen in 26 of 73 patients (36%) who received enzalutamide as second-line therapy, compared with 3 of 75 patients (4%) who received abiraterone (*P*<.0001). Serious adverse events were reported in 15 of 101 patients (15%) in group A and in 20 of 101 patients (20%) in group B, with the most common grade 3/4 adverse events being hypertension and fatigue.

Metastasis-Directed Therapy

In addition to systemic therapy, many providers are turning to metastasis-directed therapy to improve PFS in patients

with M1 CRPC. Several studies have aimed to improve our understanding of the effect of radiation therapy to oligometastatic sites. In the results from their randomized phase 2 STOMP trial, Ost and colleagues found that among patients with biochemical recurrence and evidence of at least 3 metastatic lesions, those who underwent metastasis-directed therapy had a longer 5-year ADT-free survival than did patients who underwent surveillance (HR, 0.57; 95% CI, 0.38-0.84; *P*=.06).[74] The ORIOLE trial addressed this same question but focused on patients with 1 to 3 metastatic sites.[75] In this phase 2 randomized trial, Phillips and colleagues found that patients treated with stereotactic ablative radiotherapy (SABR) were less likely to demonstrate disease progression at 6 months (7/36 patients, 19%) than were patients undergoing observation (11/18 patients, 61%; *P*=.005). A new arm of the STAMPEDE trial (M arm) will investigate the role of metastasis-directed therapy for M1 CRPC, but data have not yet been published.[67,76]

Conclusion

In the last decade, the treatment of men with advanced and metastatic prostate cancer has been revolutionized by the development of novel pharmaceuticals, advanced imaging techniques, and renewed interest in local therapy in the setting of metastatic disease. The plethora of drugs now available to treat advanced prostate cancer has created a new therapeutic dilemma: which agents to select and how to sequence these agents. Future studies will likely focus on comparisons of FDA-approved agents as well as the incorporation of advanced imaging into treatment paradigms. As survival among these patients improves, the study of prostate cancer survivorship and quality-of-life outcomes will gain even more importance. The last decade has been an exciting time for those who treat advanced prostate cancer, and we are optimistic that these advances represent only the beginning of seismic changes in the treatment landscape.

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