

Prostate Cancer, Version 4.2023

Edward M. Schaeffer, MD, PhD^{1,*}; Sandy Srinivas, MD^{2,*}; Nabil Adra, MD, MSc³; Yi An, MD⁴; Daniel Barocas, MD, MPH⁵; Rhonda Bitting, MD⁶; Alan Bryce, MD⁷; Brian Chapin, MD⁸; Heather H. Cheng, MD, PhD⁹; Anthony Victor D'Amico, MD, PhD¹⁰; Neil Desai, MD, MHS¹¹; Tanya Dorff, MD¹²; James A. Eastham, MD¹³; Thomas A. Farrington¹⁴; Xin Gao, MD¹⁰; Shilpa Gupta, MD¹⁵; Thomas Guzzo, MD, MPH¹⁶; Joseph E. Ippolito, MD, PhD¹⁷; Michael R. Kuettel, MD, MBA, PhD¹⁸; Joshua M. Lang, MD, MS¹⁹; Tamara Lotan, MD²⁰; Rana R. McKay, MD²¹; Todd Morgan, MD²²; George Netto, MD²³; Julio M. Pow-Sang, MD²⁴; Robert Reiter, MD, MBA²⁵; Mack Roach III, MD²⁶; Tyler Robin, MD, PhD²⁷; Stan Rosenfeld²⁸; Ahmad Shabsigh, MD²⁹; Daniel Spratt, MD¹⁵; Benjamin A. Teply, MD^{30,*}; Jonathan Tward, MD, PhD³¹; Richard Valicenti, MD³²; Jessica Karen Wong, MD³³; Dorothy A. Shead, MS^{34,*}; Jenna Snedeker, MS, ASCP^{34,*}; and Deborah A. Freedman-Cass, PhD^{34,*}

ABSTRACT

The NCCN Guidelines for Prostate Cancer provide a framework on which to base decisions regarding the workup of patients with prostate cancer, risk stratification and management of localized disease, post-treatment monitoring, and treatment of recurrence and advanced disease. The Guidelines sections included in this article focus on the management of metastatic castration-sensitive disease, nonmetastatic castration-resistant prostate cancer (CRPC), and metastatic CRPC (mCRPC). Androgen deprivation therapy (ADT) with treatment intensification is strongly recommended for patients with metastatic castration-sensitive prostate cancer. For patients with nonmetastatic CRPC, ADT is continued with or without the addition of certain secondary hormone therapies depending on prostate-specific antigen doubling time. In the mCRPC setting, ADT is continued with the sequential addition of certain secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies. The NCCN Prostate Cancer Panel emphasizes a shared decision-making approach in all disease settings based on patient preferences, prior treatment exposures, the presence or absence of visceral disease, symptoms, and potential side effects.

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¹Robert H. Lurie Comprehensive Cancer Center of Northwestern University;
²Stanford Cancer Institute; ³Indiana University Melvin and Bren Simon Comprehensive Cancer Center; ⁴Yale Cancer Center/Smylie Cancer Hospital;
⁵Vanderbilt-Ingram Cancer Center; ⁶Duke Cancer Institute; ⁷Mayo Clinic Comprehensive Cancer Center; ⁸The University of Texas MD Anderson Cancer Center; ⁹Fred Hutchinson Cancer Center; ¹⁰Dana-Farber/Brown and Women's Cancer Center | Mass General Cancer Center; ¹¹UT Southwest Simmons Comprehensive Cancer Center; ¹²City of Hope National Cancer Center; ¹³Memorial Sloan Kettering Cancer Center; ¹⁴Prostate Health Education Network (PHEN); ¹⁵Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; ¹⁶Abramson Cancer Center at The University of Pennsylvania; ¹⁷Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; ¹⁸Roswell Park Comprehensive Cancer Center; ¹⁹University of Wisconsin Carbone Cancer Center; ²⁰The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; ²¹UC San Diego Moores Cancer Center; ²²University of Michigan Rogel Cancer Center; ²³O'Neal Comprehensive Cancer Center at UAB; ²⁴Moffitt Cancer Center; ²⁵UCLA Jonsson Comprehensive Cancer Center; ²⁶UCSF Helen Diller Family Comprehensive Cancer Center; ²⁷University of Colorado Cancer Center; ²⁸University of California San Francisco, Patient Services Committee Chair; ²⁹The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; ³⁰Fred & Pamela Buffett Cancer Center; ³¹Huntsman Cancer Institute at the University of Utah; ³²UC Davis Comprehensive Cancer Center; ³³Fox Chase Cancer Center; and ³⁴National Comprehensive Cancer Network.

*Discussion Writing Committee Member.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Prostate Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

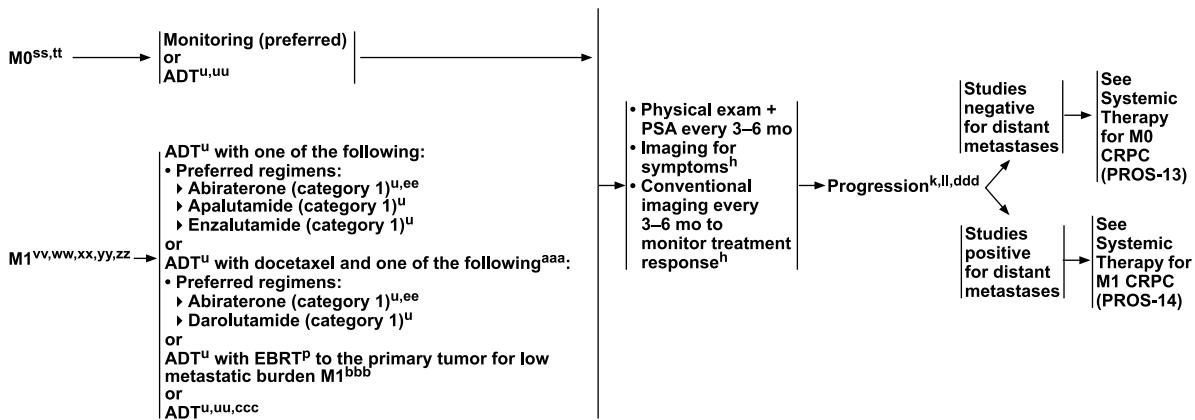
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Individual disclosures for the NCCN Prostate Cancer Panel members can be found on page 1096. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER^{TT}

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Overview

An estimated 288,300 new cases of prostate cancer will be diagnosed in the United States in 2023, accounting for 29% of new cancer cases in men.¹ It is the most common cancer in men in the United States, who currently have a 1 in 8 lifetime risk of developing prostate cancer.¹ The incidence of prostate cancer declined by approximately 40% from 2007 to 2014, but since that time has increased at a rate of 3% annually. This increase is driven by a rise in the diagnosis of regional and metastatic disease, which may be a result of declining rates of prostate specific antigen (PSA) testing that followed the 2012 United States Preventive Services Task Force (USPSTF) recommendations against it.^{2–10}

Researchers further estimate that prostate cancer will account for 11% of male cancer deaths in the United States in 2023, with an estimated 34,700 deaths.¹ The age-adjusted death rate from prostate cancer declined by 52% from 1993 to 2017, but the death rate has become more stable in recent years, with a 0.6% annual decrease from 2013 through 2020.¹ For all stages combined, the 5-year relative survival rate for prostate cancer is 97%.¹ The comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer, but death rate is also complicated by screening-related lead-time bias

and detection of indolent cancers. Maintenance of this low death rate is threatened by the rising prostate cancer incidence and diagnosis of advanced disease.

Unfortunately, large inequities exist in incidence of and mortality from prostate cancer across racial and ethnic groups. The incidence rate in Black individuals is 70% higher than in white individuals, and the mortality rate in this population is 2- to 4-times higher than all other racial and ethnic groups.¹ In addition, the mortality rate for American Indian/Alaska Native populations is higher than for white individuals.

The USPSTF released updated recommendations in 2018 that include individualized, informed decision-making regarding prostate cancer screening in men aged 55 to 69 years.¹¹ These updated recommendations may allow for a more balanced approach to prostate cancer early detection, and evidence suggests that prostate specific antigen (PSA) testing rates increased after the USPSTF's draft statement was released in 2017.¹² Better use of PSA for early detection of potentially fatal prostate cancer coupled with the use of imaging and biomarkers to improve the specificity of screening should decrease the risk of overdiagnosis (see the NCCN Guidelines for Prostate Cancer Early Detection, available at NCCN.org). This reduced overdiagnosis along with the use of active surveillance in appropriate patients should reduce overtreatment

FOOTNOTES

^h See Principles of Imaging (PROS-E*).^k Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.^l See Principles of Radiation Therapy (PROS-G).^u See Principles of Androgen Deprivation Therapy (PROS-I).^{ee} The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).^{ll} Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluorocholine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E*).^{rr} The term "castration-sensitive" is used to define patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.^{ss} PSA DT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.^{tt} Patients with a life expectancy ≤5 years can consider observation. See Principles of Active Surveillance and Observation (PROS-F*).^{uu} Intermittent ADT can be considered for patients with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-I).^{vv} EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.^{ww} ADT alone (see PROS-I) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.^{xx} Tumor and germline testing for homologous recombination repair gene mutations (HRM) is recommended and tumor testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR) can be considered. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C*).
^{yy} Stereotactic body RT (SBRT) to metastases can be considered in patients with oligometastatic progression where progression-free survival (PFS) is the goal.^{zz} Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-I.^{aaa} The panel encourages ADT with docetaxel and either abiraterone or abiraterone for patients with high-volume disease who are fit for chemotherapy. See Principles of Non-Hormonal Systemic Therapy (PROS-J).^{bbb} EBRT to the primary tumor is associated with an overall survival benefit in patients with low metastatic burden at the time of diagnosis of metastatic disease, which is defined by conventional imaging as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis (Ali A, et al. JAMA Oncol 2021;7:555-563). See Principles of Radiation Therapy (PROS-G).^{ccc} ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy.^{ddd} Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-sensitive disease.

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and preserve the relatively low rates of prostate cancer mortality.

Management of Metastatic Castration-Sensitive Prostate Cancer

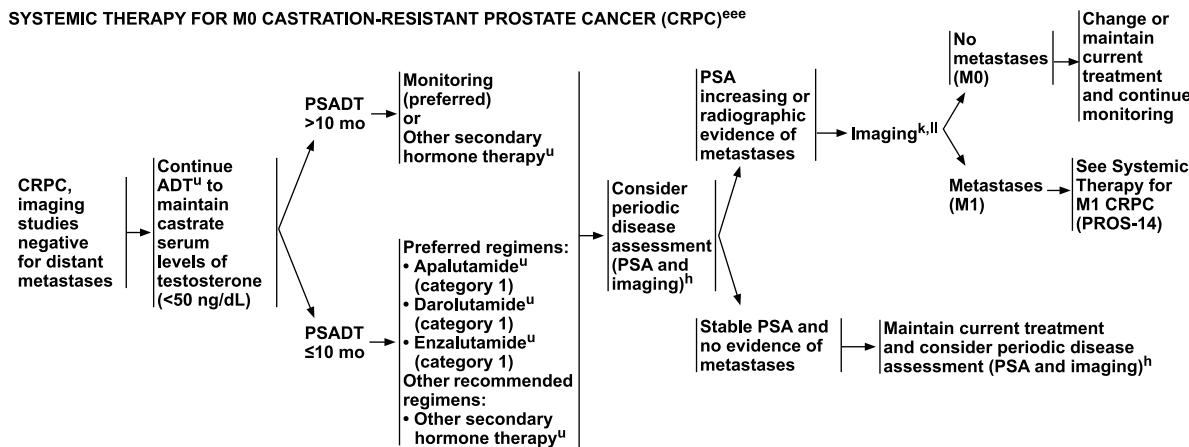
Androgen deprivation therapy (ADT) with treatment intensification is strongly recommended for patients with metastatic castration-sensitive prostate cancer. The use of ADT monotherapy in this setting is discouraged unless there are clear contraindications to combination therapy. Treatment intensification options include doublet therapy of ADT with abiraterone, apalutamide, or enzalutamide; triplet therapy of ADT with docetaxel and abiraterone or darolutamide; or ADT with external beam radiation therapy (EBRT) to the primary tumor for low-metastatic burden. The data supporting doublet or triplet therapy in this setting are discussed subsequently. The doublet and triplet therapies are all category 1, preferred options; the fine-particle formulation of abiraterone (discussed in "Abiraterone Acetate in M1 CRPC," page 1076) can be added to ADT as a category 2B, other recommended option. ADT with EBRT to the primary tumor for patients with low metastatic burden is discussed in "EBRT to the Primary Tumor in Low-Metastatic-Burden M1 Disease" (available, in these guidelines, at NCCN.org).

Doublet Therapies for Castration-Sensitive Prostate Cancer

Abiraterone Acetate in Castration-Sensitive Prostate Cancer

In February 2018, the FDA approved abiraterone in combination with prednisone for metastatic castration-sensitive prostate cancer. This approval was based on 2 randomized phase III clinical trials of abiraterone and low-dose prednisone plus ADT in patients with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease (STAMPEDE and LATITUDE) that demonstrated improved overall survival (OS) over ADT alone.¹³

In LATITUDE, 1,199 patients with high-risk, metastatic, castration-sensitive prostate cancer were randomized to abiraterone with prednisone 5 mg once daily or matching placebos. High-risk disease was defined as at least 2 of the following: Gleason score 8–10, ≥3 bone metastases, and visceral metastases.¹³ Efficacy was demonstrated at the first interim analysis, and the trial was unblinded. The primary endpoint of OS was met and favored abiraterone (hazard ratio [HR], 0.62; 95% CI, 0.51–0.76; $P<.0001$). Estimated 3-year OS rates improved from 49% to 66% at 30 months follow-up. Secondary endpoints were improved and included delayed castration-resistant radiographic progression (from median 14.8–33.2 months), PSA progression (7.4–33.2 months), time to pain progression, and initiation of chemotherapy.



^hSee Principles of Imaging (PROS-E*).

^kBecause of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

^uSee Principles of Androgen Deprivation Therapy (PROS-I).

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After the first interim analysis, 72 patients crossed over from placebo to abiraterone. Final OS analysis of LATITUDE after a median follow-up of 51.8 months showed median OS was significantly longer in the abiraterone group than in the placebo group (53.3 vs 36.5 months; HR, 0.66; 95% CI, 0.56–0.78; $P<.0001$).¹⁴

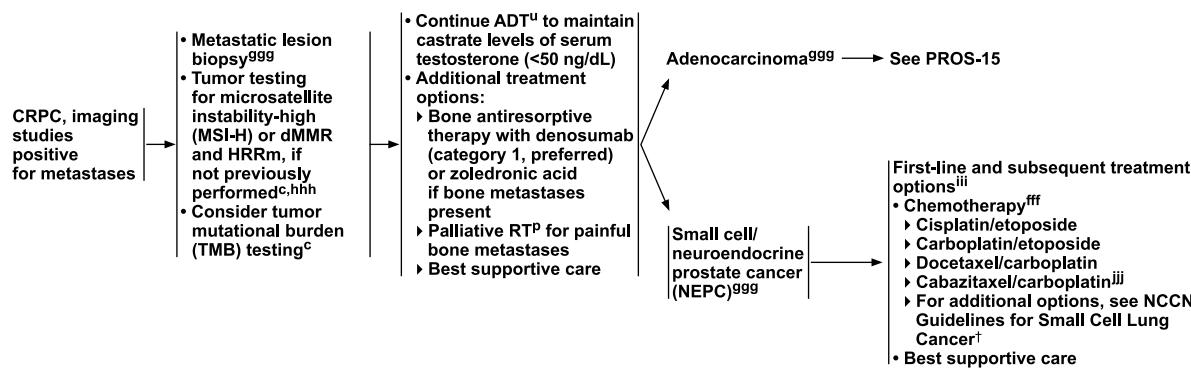
Adverse events were higher with abiraterone and prednisone but were generally mild in nature and largely related to mineralocorticoid excess (ie, hypertension, hypokalemia, edema), hormonal effects (ie, fatigue, hot flushes), and liver toxicity.¹³ Cardiac events, such as atrial fibrillation, were rare but slightly increased with abiraterone. The overall discontinuation rate due to side effects was 12%. Patient-reported outcomes were improved with the addition of abiraterone, with improvements in pain intensity progression, fatigue, functional decline, prostate cancer-related symptoms, and overall health-related quality of life (QOL).¹⁵ A limitation of this trial is that only 27% of placebo-treated patients received abiraterone or enzalutamide at progression, and only 52% of these patients received any life-prolonging therapy.¹³

The second randomized trial (STAMPEDE) of 1,917 patients with castration-sensitive prostate cancer showed similar OS benefits.¹⁶ However, unlike LATITUDE, STAMPEDE eligibility permitted patients with high-risk N0,M0 disease (2 of 3 high-risk factors: stage T3/4, PSA

^{II}Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E*).

^{eee}CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, et al. J Clin Oncol 2008;26:1148–1159.

>40, or Gleason score 8–10; n=509), or N1,M0 disease (pelvic nodal metastases; n=369) in addition to patients with M1 disease, who made up the majority of patients (n=941). Most patients were newly diagnosed, and a minority had recurrent, high-risk, or metastatic disease after local therapy (n=98). Thus, STAMPEDE was a heterogeneous mix of patients with high-risk, nonmetastatic, node-positive, or M1 disease. In patients with M1 disease, treatment with abiraterone plus prednisone was continued until progression. In patients with N1 or M0 disease, 2 years of abiraterone plus prednisolone was used if curative-intent EBRT was used. OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; $P<.0001$) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status. The survival benefit of abiraterone was larger in patients <70 years of age than those ≥70 years (HR, 0.94 vs HR, 0.51). Patients ≥70 years also experienced increased toxicities, which suggests heterogeneity in clinical benefits by age and comorbidity. The secondary endpoint of failure-free survival, which included PSA recurrence, was improved overall (HR, 0.29; $P<.0001$) and in all subgroups regardless of M1 (HR, 0.31), N1 (HR, 0.29), or M0 (HR, 0.21) status. No heterogeneity for failure-free survival was observed based on subgroups or by age. In this trial, subsequent life-prolonging therapy was received by

SYSTEMIC THERAPY FOR M1 CRPC^{eee}^c See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C*).^d See Principles of Radiation Therapy (PROS-G).^{eee} CRPC is prostate cancer that progresses clinically, radiographically, or

biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, et al. J Clin Oncol 2008;26:1148-1159.

^{fff} See Principles of Non-Hormonal Systemic Therapy (PROS-J)^{ggg} Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed.^{hhh} Germline testing for HRRm is recommended if not performed previously. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C*).*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.Version 4.2023, 09/07/23 © 2023 National Comprehensive Cancer Network® (NCCN®). All rights reserved.
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58% of those in the control group, which included 22% who received abiraterone and 26% who received enzalutamide. Thus, these data reflect a survival advantage of initial abiraterone in newly diagnosed patients compared with deferring therapy to the castration-resistant prostate cancer (CRPC) setting.

Adverse events in STAMPEDE were similar to those reported in LATITUDE, but were increased in patients ≥ 70 years, with higher incidences of grade 3–5 adverse events with abiraterone (47% vs 33%) and 9 versus 3 treatment-related deaths. Severe hypertension or cardiac disorders were noted in 10% of patients and grade 3–5 liver toxicity in 7%, which illustrates the need for blood pressure and renal and hepatic function monitoring.

Taken together, these data led the NCCN Prostate Cancer Panel to recommend abiraterone with 5 mg once daily prednisone as a treatment option with ADT for patients with newly diagnosed, M1, castration-sensitive prostate cancer (category 1). Alternatively, the fine-particle formulation of abiraterone can be used (category 2B; see “Abiraterone Acetate in M1 CRPC,” page 1076).

Abiraterone can be given at 250 mg/day and administered after a low-fat breakfast as an alternative to the dose of 1,000 mg/day after an overnight fast (see “Abiraterone Acetate in M1 CRPC,” page 1076).¹⁷ The cost savings may reduce financial toxicity and improve adherence.

Apalutamide in Castration-Sensitive Prostate Cancer

The double-blind phase III TITAN clinical trial randomized 1,052 patients with metastatic, castration-sensitive prostate cancer to ADT with apalutamide (240 mg/d) or placebo.¹⁸ Participants were stratified by Gleason score at diagnosis, geographic region, and previous docetaxel treatment. The median follow-up was 22.7 months. Both primary endpoints were met: radiographic progression-free survival (PFS) (68.2% vs 47.5% at 24 months; HR for radiographic progression or death, 0.48; 95% CI, 0.39–0.60; $P < .001$) and OS (82.4% vs 73.5% at 24 months; HR for death, 0.67; 95% CI, 0.51–0.89; $P = .005$). Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease. Health-related QOL was maintained during treatment.¹⁹ At final analysis of TITAN, median OS was improved with apalutamide plus ADT compared with ADT alone after a median follow-up of 44 months (no response vs 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; $P < .001$).²⁰

Apalutamide is a category 1 option for patients with M1 castration-sensitive prostate cancer. The FDA approved this indication in September of 2019.

Enzalutamide in Castration-Sensitive Prostate Cancer

The open-label randomized phase III ENZAMET clinical trial compared enzalutamide (160 mg/d) plus ADT

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{iii,kkk,III}

No prior docetaxel/no prior novel hormone therapy^{mmm}	Prior novel hormone therapy/no prior docetaxel^{mmm,ttt}
<ul style="list-style-type: none"> Preferred regimens <ul style="list-style-type: none"> Abiraterone^{u,nnn,ooo} (category 1) Docetaxel^{fff,ppp} (category 1) Enzalutamide^u (category 1) Useful in certain circumstances <ul style="list-style-type: none"> Niraparib/abiraterone^{u,fff,zzz} for BRCA mutation (category 1) Olaparib/abiraterone^{u,fff,nnn,qqq} for BRCA mutation (category 1) Radium-223^{ttt} for symptomatic bone metastases (category 1) Sipuleucel-T^{fff,sss} (category 1) Talazoparib/enzalutamide for HRRm^{u,fff,yyy} (category 1) Other recommended regimens <ul style="list-style-type: none"> Other secondary hormone therapy^u 	<ul style="list-style-type: none"> Preferred regimens <ul style="list-style-type: none"> Docetaxel (category 1)^{fff} Useful in certain circumstances <ul style="list-style-type: none"> Cabazitaxel/carboplatin^{fff,jjj} Niraparib/abiraterone^{u,fff,zzz} for BRCA mutation (category 2B) Olaparib for HRRm^{uuu} (category 1) Radium-223^{ttt} for symptomatic bone metastases (category 1) Rucaparib for BRCA mutation^{vvv} Sipuleucel-T^{fff,sss} Talazoparib/enzalutamide for HRRm^{u,fff,yyy} (category 2B) Other recommended regimens <ul style="list-style-type: none"> Abiraterone^{u,nnn} Abiraterone^u + dexamethasone^{nnn,www} Enzalutamide^u Other secondary hormone therapy^u
Prior docetaxel/no prior novel hormone therapy^{mmm}	Prior docetaxel and prior novel hormone therapy^{mmm,ttt}
<ul style="list-style-type: none"> Preferred regimens <ul style="list-style-type: none"> Abiraterone^{u,nnn} (category 1) Cabazitaxel^{fff} Enzalutamide^u (category 1) Useful in certain circumstances <ul style="list-style-type: none"> Cabazitaxel/carboplatin^{fff,jjj} Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{fff} Niraparib/abiraterone^{u,fff,zzz} for BRCA mutation Olaparib/abiraterone^{u,fff,nnn,qqq} for BRCA mutation Radium-223^{ttt} for symptomatic bone metastases (category 1) Sipuleucel-T^{fff,sss} Talazoparib/enzalutamide for HRRm^{u,fff,yyy} Other recommended regimens <ul style="list-style-type: none"> Other secondary hormone therapy^u 	<ul style="list-style-type: none"> Useful in certain circumstances <ul style="list-style-type: none"> Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) for PSMA-positive metastases^{xxx} (category 1) (The following systemic therapies are category 2B if visceral metastases are present) <ul style="list-style-type: none"> Preferred regimens <ul style="list-style-type: none"> Cabazitaxel^{fff,ooo} (category 1) Docetaxel rechallenge^{fff} Useful in certain circumstances <ul style="list-style-type: none"> Cabazitaxel/carboplatin^{fff,jjj} Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{fff} Olaparib for HRRm^{ooo,uuu} (category 1) Pembrolizumab for MSI-H, dMMR, or TMB ≥ 10 mut/Mb^{fff} Radium-223^{ttt} for symptomatic bone metastases^{ooo} (category 1) Rucaparib for BRCA mutation^{vvv} Other recommended regimens <ul style="list-style-type: none"> Abiraterone^{u,nnn} Enzalutamide^u Other secondary hormone therapy^u

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(luteinizing hormone-releasing hormone [LHRH] analog or surgical castration) with a first-generation antiandrogen (bicalutamide, nilutamide, or flutamide) plus ADT in 1,125 patients with metastatic castration-sensitive prostate cancer.²¹ Stratification was by volume of disease, planned use of early docetaxel, planned use of bone antiresorptive therapy, comorbidity score, and trial site. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; $P=.002$). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS. An additional analysis was triggered at 470 deaths.²² After a median follow-up of 68 months, the 5-year OS rate was again lower in the first-generation antiandrogen group than in the enzalutamide group (HR, 0.70; 95% CI, 0.58–0.84; $P<.0001$). The median OS was not reached.

In the double-blind randomized phase III ARCHES clinical, 1,150 patients with metastatic castration-sensitive prostate cancer were randomized to receive ADT with either enzalutamide (160 mg/d) or placebo. Participants were stratified by disease volume and prior docetaxel use. The primary endpoint was radiographic PFS, which was improved in the enzalutamide group after a median follow-up of 14.4 months (19.0 months vs not reached; HR, 0.39; 95% CI, 0.30–0.50; $P<.001$).²³ At the final, prespecified

OS analysis, median OS was not met in either group, but a 34% reduction in the risk of death was observed in those receiving enzalutamide vs placebo (HR, 0.66; 95% CI, 0.53–0.81; $P<.001$).²⁴ This result could be an underestimate of the effect of enzalutamide, since approximately 32% of the patients assigned placebo crossed over to enzalutamide after unblinding.

The safety of enzalutamide in these trials was similar to that seen in previous trials in the castration-resistant setting. Adverse events associated with enzalutamide in these trials included fatigue, seizures, and hypertension.^{21,23}

Enzalutamide is a category 1 option for patients with M1 castration-sensitive prostate cancer. The FDA approved this indication in December 2019.

Docetaxel in Castration-Sensitive Prostate Cancer

Docetaxel has been studied as an upfront option for patients with castration-sensitive prostate cancer and distant metastases based on results from 2 phase III trials (ECOG 3805/CHAARTED and STAMPEDE).^{25,26} CHAARTED randomized 790 patients with metastatic, castration-sensitive prostate cancer to docetaxel (75 mg/m² intravenous every 3 weeks \times 6 doses) plus ADT or ADT alone.²⁶ After a median follow-up of 53.7 months, the patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 vs 47.2 months; HR, 0.72; 95% CI, 0.59–0.89; $P=.002$).²⁷

FOOTNOTES

^u See Principles of Androgen Deprivation Therapy (PROS-I).

^{fff} See Principles of Non-Hormonal Systemic Therapy (PROS-J).

ⁱⁱⁱⁱ Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-15. See Principles of Imaging (PROS-E) and Discussion.

^{jjj} Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

^{kkk} Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.

^{lll} Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

^{mm} Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.

ⁿⁿⁿ The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).

^{ooo} The noted category applies only if there are no visceral metastases.

^{ppp} Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

^{qqq} Olaparib with abiraterone is an option for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy and who have not yet had treatment in the setting of CRPC.

^{rrr} Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-G).

^{sss} Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, and ECOG performance status 0–1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/NEPC.

^{ttt} Consider AR-V7 testing to help guide selection of therapy (See Discussion).

^{uuu} Olaparib is a treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC) and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) who have been treated previously with androgen receptor-directed therapy. However, efficacy appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis. There may be heterogeneity of response to olaparib for non-*BRCA* mutations based on the specific gene mutation. (See Discussion).

^{vvv} Rucaparib is a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

^{www} Switching from prednisone to dexamethasone 1 mg/day can be considered for patients with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy. Romero-Laorden N, et al. Br J Cancer 2018;119:1052-1059 and Fenoux C, et al. BJU Int 2019;123:300-306.

^{xxx} Lu-177-PSMA-617 is a treatment option for patients with ≥1 PSMA-positive lesion and/or metastatic disease that is predominantly PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy. Sartor E, et al. N Engl J Med 2021; 385:1091-1103. See Principles of Radiation Therapy (PROS-G).

^{yyy} Talazoparib plus enzalutamide is a treatment option for patients with metastatic CRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC, depending on prior treatment in other disease settings (PROS-15). There may be heterogeneity of response based on the specific gene mutation. (See Discussion). Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy is controversial because a benefit of this combination overuse of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

^{zzz} Niraparib plus abiraterone (combination tablet) is a treatment option for patients with metastatic CRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of metastatic CRPC, depending on prior treatment in other disease settings (see PROS-15). Use of niraparib/abiraterone for those who have received prior novel hormone therapy is controversial because a benefit of this combination overuse of a PARP inhibitor alone has not been shown in this setting, but responses are likely. The fine-particle formulation of abiraterone can be given with single-agent niraparib as a substitute for the combination niraparib/abiraterone tablet (category 2B; other recommended option).

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PROS-15A

Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.63; 95% CI, 0.50–0.79; *P*<.001). Patients with low metastatic burden in CHARTED did not derive a survival benefit from the inclusion of docetaxel (HR, 1.04; 95% CI, 0.70–1.55; *P*=.86).

The STAMPEDE trial, a multiarm, multistage phase III trial, included patients with both M0 and M1 castration-sensitive prostate cancer.²⁵ The results in the M1 population confirmed the survival advantage of adding docetaxel (75 mg/m² intravenous every 3 weeks × 6 doses) to ADT seen in the CHARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1,087 patients with metastatic disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT-plus-docetaxel arm versus 3.6 years in the ADT-only arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHARTED).

Patients with low metastatic burden did not have definitively improved survival outcomes in the ECOG CHARTED study or a similar European trial (GETUG-AFU 15).^{26,28,29} Furthermore, the triplet options of ADT with docetaxel and either abiraterone or darolutamide showed improved OS over ADT with docetaxel (see subsequent sections). The panel therefore does not include docetaxel with ADT as an option for patients with metastatic

castration-sensitive prostate cancer. Rather, patients with high-volume castration-sensitive metastatic prostate cancer who are fit for chemotherapy should be considered for triplet therapy.

Triplet Therapies for Castration-Sensitive Prostate Cancer

Data from the PEACE-1 and ARASENS trials indicate that triplet therapies of ADT with docetaxel and a novel hormone therapy—either abiraterone or darolutamide—improve OS over ADT with docetaxel.^{30,31} These trials are discussed in subsequent sections. Both of these combinations are included as category 1, preferred options for patients with metastatic castration-sensitive prostate cancer, and their use is encouraged for patients with high-volume de novo disease who are fit for chemotherapy.

Docetaxel Plus Abiraterone in Castration-Sensitive Prostate Cancer

PEACE-1 was an international, open-label, randomized, phase III study conducted in 7 European countries.³⁰ Using a 2×2 factorial design, 1,173 patients with de novo metastatic prostate cancer were randomized at a 1:1:1 ratio to standard of care (ADT alone or with docetaxel), standard of care with radiation therapy, standard of care with abiraterone, or standard of care with radiation and

PRINCIPLES OF RADIATION THERAPY

Radiopharmaceutical Therapy

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in patients with visceral metastases or bulky nodal disease (>3–4 cm). Radium-223 differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (ie, 2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered IV once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin $\geq 10\text{ g/dL}$.
- Prior to subsequent doses, patients must have ANC $\geq 1 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$ (per label). Radium-223 should be discontinued if a delay of 6–8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.
- Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except in a clinical trial.
- Radium-223 may increase fracture risk when given concomitantly with abiraterone.
- Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT.
- Concomitant use of denosumab or zoledronic acid is recommended; it does not interfere with the beneficial effects of radium-223 on survival.

- Lu-177-PSMA-617
 - Lu-177-PSMA-617 is a beta-emitting radiopharmaceutical that selectively binds to PSMA receptors on prostate cancer cells. In patients with PSMA-positive disease, Lu-177-PSMA-617 has been shown to improve overall survival in patients with progressive mCRPC previously treated with androgen receptor inhibitors and taxane chemotherapy. Sartor O, et al. *N Engl J Med* 2021;385:1091–1103.
 - Lu-177-PSMA-617 is not recommended in patients with dominant PSMA-negative lesions. PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components $\geq 1.0\text{ cm}$, lymph nodes $\geq 2.5\text{ cm}$ in short axis, and solid organ metastases $\geq 1.0\text{ cm}$ in size.
 - Lu-177-PSMA-617 is typically administered IV 200 mCi (7.4 GBq) every 6 weeks for a total of 6 treatments by an appropriately licensed facility, usually in nuclear medicine or RT departments. Patients should be well-hydrated during treatment. Because Lu-177 also emits gamma radiation, appropriate precautions should be taken to minimize exposure to personnel administering the radiopharmaceutical. Treatment rooms should be monitored for potential contamination following treatments, and patients should be provided written instructions regarding radiation safety precautions following treatment.
 - The most frequently reported side effects from Lu-177-PSMA-617 include fatigue (43%), dry mouth (39%), nausea (35%), and anemia (32%).
 - Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177-PSMA-617, the panel believes that F-18 piflufolastat PSMA and F-18 flutufolastat PSMA can also be used in the same space due to multiple reports describing the equivalency of these imaging agents in:
 - ◊ PSMA molecular recognition motifs,
 - ◊ normal organ biodistribution, and
 - ◊ detection accuracy of prostate cancer lesions.

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abiraterone. The 2 primary endpoints of the trial were radiographic PFS and OS. Adjusted Cox regression modeling showed no interaction between abiraterone and radiation therapy, so data were pooled for the analysis of abiraterone efficacy. Consistent with results of older studies, radiographic PFS was longer in patients who received abiraterone than in those that did not (HR, 0.54; 99.9% CI, 0.41–0.71; $P < .0001$) as was OS (HR, 0.82; 95.1% CI, 0.69–0.98; $P = .030$).

As part of the analysis, the efficacy of abiraterone was assessed in the population that received docetaxel. As in the overall population, radiographic PFS (HR, 0.50; 99.9% CI, 0.34–0.71; $P < .0001$) and OS (HR, 0.75; 95.1% CI, 0.59–0.95; $P = .017$) were longer in those receiving all three therapies compared with those only receiving ADT and docetaxel. The populations receiving the triplet and doublet therapies experienced similar rates of neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥ 3 adverse events occurred 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.

Docetaxel Plus Darolutamide in Castration-Sensitive Prostate Cancer

The international, phase III trial ARASENS trial, the second phase III trial evaluating a triplet, randomized 1,306

patients with metastatic castration-sensitive prostate cancer to receive ADT and docetaxel with either darolutamide or matching placebo.³¹ The primary end point, OS, was improved in the darolutamide group at 4 years (62.7%; 95% CI, 58.7–66.7) compared with the placebo group (50.4%; 95% CI, 46.3–54.6). The risk of death was lower in the darolutamide group by about 32% (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$). The addition of darolutamide also showed significant benefits over placebo for secondary efficacy end points, including time to CRPC (HR, 0.36; 95% CI, 0.30 to 0.42; $P < .001$), skeletal event-free survival (HR, 0.61; 95% CI, 0.52 to 0.72; $P < .001$), and time to initiation of subsequent systemic antineoplastic therapy (HR, 0.39; 95% CI, 0.33 to 0.46; $P < .001$).

Adverse events of any grade, grade 3–5 adverse events, and serious adverse events occurred at similar incidence levels between the 2 arms. Many of these were known effects of docetaxel. The most frequent adverse events were alopecia (40.5% of patients in the darolutamide arm vs 40.6% with placebo), neutropenia (39.3% vs 38.8%), fatigue (33.1% vs 32.9%), and anemia (27.8% vs 25.1%). Exceptions were rash (16.6% vs 13.5%) and hypertension (13.7% vs 9.2%), which are known effects of androgen receptor pathway inhibitors and were more frequent in the darolutamide group.

The FDA approved this indication in August 2022.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for M0 PSA Persistence/Recurrence After RP or EBRT (ADT for M0 Castration-Sensitive Disease)

- The timing of ADT for patients whose only evidence of cancer after definitive treatment is an increasing PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.
- Some patients are candidates for salvage therapy after PSA persistence/recurrence. See PROS-10* and PROS-11*.
- Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation.
- Patients who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm. An unplanned subset analysis showed that patients with Grade Group 4 or 5 prostate cancer in the continuous arm had a median overall survival that was 14 months longer (8 years) than those in the intermittent arm (6.8 years).
- ADT options are:
 - ▷ M0 RP PSA persistence/recurrence:
 - ◊ EBRT +/- neoadjuvant, concurrent, and/or adjuvant ADT [See ADT for Clinically Localized (N0,M0) Disease]
 - ◊ EBRT + LHRH agonist or degarelix with abiraterone (studies positive for pelvic recurrence only)
 - ▷ M0 RT recurrence, biopsy negative or M0 PSA recurrence after progression on salvage EBRT:

- ◊ Orchiectomy
- ◊ LHRH agonist alone
 - Goserelin, leuprorelin, or triptorelin
- ◊ LHRH agonist (as above) plus first-generation antiandrogen
 - Nilutamide, flutamide, or bicalutamide
- ◊ LHRH antagonist
 - Degarelix or relugolix

▷ Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease].

ADT for Metastatic Castration-Sensitive Disease

- ADT with treatment intensification is preferred for most patients with metastatic prostate cancer. ADT alone is appropriate for some patients.
- Treatment options for patients with M1 castration-sensitive disease are:
 - ▷ ADT alone (orchectomy, LHRH agonist, LHRH agonist plus first-generation antiandrogen, or LHRH antagonist)
 - ◊ LHRH agonists: Goserelin, leuprorelin, or triptorelin
 - ◊ First-generation antiandrogens: Nilutamide, flutamide, or bicalutamide
 - ◊ A first-generation antiandrogen must be given with LHRH agonist for 27 days to prevent testosterone flare if metastases are present in weight-bearing bone
 - ▷ Orchectomy plus abiraterone, enzalutamide, or apalutamide
 - ▷ Orchectomy plus docetaxel and abiraterone or darolutamide
 - ▷ LHRH agonist (as above) plus abiraterone, enzalutamide, or apalutamide
 - ▷ LHRH agonist (as above) plus docetaxel and abiraterone or darolutamide
 - ▷ Degarelix plus abiraterone, enzalutamide, or apalutamide
 - ▷ Degarelix plus docetaxel and abiraterone or darolutamide
 - ▷ Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease].
- When EBRT to primary is given with ADT in low metastatic burden M1, the options are LHRH agonist, LHRH antagonist, and orchectomy.
- Two randomized phase 3 clinical trials of abiraterone with prednisone plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved overall survival over ADT alone. Adverse events were higher with abiraterone and prednisone but were generally mild in nature and were largely related to mineralocorticoid excess (ie, hypertension, hypokalemia, edema), hormonal effects (ie, fatigue, hot flushes), and liver toxicity. Cardiac events, severe hypertension, and liver toxicity were increased with abiraterone.

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Progression to and Management of CRPC

Most advanced disease eventually stops responding to traditional ADT and is categorized as castration-resistant (also known as castration-recurrent). CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).³² Patients whose disease progresses to CRPC during primary ADT should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL; <1.7 nmol/L). Imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, overall patient health, PSA velocity, and Gleason grade.

For patients who develop CRPC, ADT with an LHRH agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL).

Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider monitoring with continued ADT if PSA doubling time (PSADT) is greater than 10 months (preferred), because these patients will have a relatively indolent disease history.³³ Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (\leq 10 months) as described subsequently.

For patients who develop mCRPC, metastatic lesion biopsy is recommended, as is microsatellite instability

(MSI)/mismatch repair (MMR) testing, if not previously performed. If MSI-high (MSI-H) or deficient MMR (dMMR) is found, referral to genetic counseling should be made to assess for the possibility of Lynch syndrome. These patients should also have germline and tumor testing to check for mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, *CDK12*) if not done previously.³⁴ This information may be used for genetic counseling, early use of platinum chemotherapy, or understanding eligibility for biomarker-directed treatments or clinical trials. Tumor mutation burden (TMB) testing should also be considered for patients with mCRPC to inform possible use of pembrolizumab in later lines of therapy (see “Pembrolizumab,” page 1084).

ADT is continued in patients with mCRPC while additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, are sequentially applied, as discussed in the subsequent sections; all patients should receive best supportive care. The panel defined treatment options for patients with mCRPC based on previous exposure to docetaxel and to a novel hormone therapy. Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- A double-blind randomized phase 3 clinical trial of apalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved overall survival over ADT alone. Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease.
- An open-label randomized phase 3 clinical trial of enzalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved overall survival over ADT alone. In a separate double-blind randomized phase 3 clinical trial, enzalutamide reduced the risk of metastatic progression or death compared with placebo and showed an overall survival benefit. Adverse events associated with enzalutamide included fatigue, seizures, and hypertension.
- A phase 3 trial compared continuous ADT to intermittent ADT, but the study could not demonstrate non-inferiority for survival. However, quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months of ADT compared to the continuous ADT arm.
- In addition, three meta-analyses of randomized controlled trials failed to show a difference in survival between intermittent and continuous ADT.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

Secondary Hormone Therapy for M0 or M1 CRPC

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone (<50 ng/dL) should be maintained by continuing LHRH agonist or degarelix while additional therapies are applied.
- Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by conventional imaging, M0 CRPC vs. M1 CRPC, and whether or not the patient is symptomatic.

- Administration of secondary hormonal therapy can include:
 - Second-generation antiandrogen
 - ◊ Apalutamide (for M0 and PSADT ≤10 months)
 - ◊ Darolutamide (for M0 and PSADT ≤10 months)
 - ◊ Enzalutamide (for M0 and PSADT ≤10 months or M1)
 - Androgen metabolism inhibitor
 - ◊ Abiraterone + prednisone (for M1 only)
 - ◊ Fine-particle abiraterone + methylprednisolone (for M1 only)
 - Other secondary hormone therapy (for M0 or M1)
 - ◊ First-generation antiandrogen (nilutamide, flutamide, or bicalutamide)
 - ◊ Corticosteroids (hydrocortisone, prednisone, or dexamethasone)
 - ◊ Antiandrogen withdrawal
 - ◊ Ketoconazole plus hydrocortisone
- Abiraterone should be given with concurrent steroid, either prednisone 5 mg PO twice daily for the standard formulation or methylprednisolone 4 mg PO twice daily for the fine-particle formulation.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed apalutamide (240 mg/day) improved the primary endpoint of metastasis-free survival over placebo (40.5 months vs. 16.2 months). After a median follow-up of 52 months, final overall survival analysis showed an improved median overall survival with apalutamide versus placebo (73.9 months vs. 59.9 months). Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs. 2%). Bone support should be used in patients receiving apalutamide.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed enzalutamide (160 mg/day) improved the primary endpoint of metastasis-free survival over placebo (36.6 months vs. 14.7 months). Median overall survival was longer in the enzalutamide group than in the placebo group (67.0 months vs. 56.3 months). Adverse events included falls and nonpathologic fractures (17% vs. 8%), hypertension (12% vs. 5%), major adverse cardiovascular events (5% vs. 3%), and mental impairment disorders (5% vs. 2%). Bone support should be used in patients receiving enzalutamide.

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The decision to initiate therapy in the CRPC setting after disease progression on one or more treatments should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to therapeutic agents should be considered. Data to inform the optimal sequence for delivery of these agents in patients with mCRPC is limited (see “Sequencing of Therapy in CRPC,” page 1091). Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects.

NCCN recommends that patients being treated for CRPC be closely monitored with radiologic imaging (ie, CT, bone imaging), PSA tests, and clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerance, with consideration of the fact that even in cases in which PSA remains undetectable, bone imaging may reveal progression.^{35,36} The sequential use of these agents is reasonable in a patient who remains a candidate for further systemic therapy. Clinical trial and best supportive care are additional options.

Secondary Hormone Therapy for CRPC

Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of

patients receiving ADT.^{37,38} Androgen signaling consequent to nongonadal sources of androgen in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the nonmetastatic and mCRPC setting dramatically changed the paradigm of CRPC treatment.

Abiraterone Acetate in M1 CRPC

In April 2011, the FDA approved the androgen synthesis inhibitor, abiraterone, in combination with low-dose prednisone, for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel.

FDA approval in the post-docetaxel, mCRPC setting was based on the results of a phase III, randomized, placebo-controlled trial (COU-AA-301) in patients with mCRPC previously treated with docetaxel-containing regimens.^{39,40} Patients were randomized to receive either abiraterone 1,000 mg orally once daily (n=797) or placebo once daily (n=398), and both arms received daily prednisone. In the final analysis, median survival was 15.8 versus 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86; P<.0001).⁴⁰ Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.^{40,41}

FDA approval in the pre-docetaxel setting occurred in December 2012 and was based on the randomized

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- A phase 3 study of patients with M0 CRPC and a PSA DT \leq 10 months showed darolutamide (600 mg twice daily) improved the primary endpoint of metastasis-free survival over placebo (40.4 months vs. 18.4 months). Overall survival at 3 years was 83% (95% CI, 80–86) in the darolutamide group compared with 77% (95% CI, 72–81) in the placebo group. Adverse events that occurred more frequently in the treatment arm included fatigue (12.1% vs. 8.7%), pain in an extremity (5.8% vs. 3.2%), and rash (2.9% vs. 0.9%). The incidence of fractures was similar between darolutamide and placebo (4.2% vs. 3.6%).
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone and low-dose prednisone (5 mg BD) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. An improvement in overall survival was demonstrated. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
- A phase 3 study of docetaxel-sensitive patients with M1 CRPC showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and overall survival. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of patients on enzalutamide).
- For symptomatic patients with M1 CRPC, all secondary hormone options listed above are allowed, but initial use of docetaxel may be preferred. Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in patients who had no or minimal symptoms due to M1 CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Both abiraterone and enzalutamide are approved in this pre-docetaxel setting and have category 1 recommendations. Both drugs are suitable options for patients who are not good candidates to receive docetaxel.

- In the post-docetaxel M1 CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized controlled trials. Therefore, each agent has a category 1 recommendation.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/day enzalutamide improved PFS compared to 50 mg/day bicalutamide in patients with treatment-naïve M1 CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side effect profiles of the agents and the increased cost of enzalutamide.
- Evidence-based guidance on the sequencing of agents in either pre- or post-docetaxel remains limited.

ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy \leq 5 Years

- Treatment for patients whose cancer progressed on observation of localized disease is LHRH agonist or antagonist or orchectomy.

Optimal ADT

- Medical castration (ie, LHRH agonist or antagonist) and surgical castration (ie, bilateral orchectomy) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be coadministered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended.
- No clinical data support the use of finasteride or dutasteride with combined androgen blockade.
- Patients who do not achieve adequate suppression of serum testosterone (<50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. Consider monitoring testosterone levels 12 weeks after first dose of LHRH therapy, then upon increase in PSA. The optimal level of serum testosterone to affect "castration" has yet to be determined.

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phase III COU-AA-302 trial of abiraterone and prednisone (n=546) versus prednisone alone (n=542) in patients with asymptomatic or minimally symptomatic, mCRPC.⁴² Most participants in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary endpoint of radiographic PFS was improved by treatment from 8.3 to 16.5 months (HR, 0.53; $P < .001$). OS was improved at final analysis with a median follow-up of 49.2 months (34.7 vs 30.3 months; HR, 0.81; 95% CI, 0.70–0.93; $P = .003$).⁴³ Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment; PSA declines (62% vs 24% with $>50\%$ decline) and radiographic responses (36% vs 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone ($>5\%$) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were

increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%).

In May 2018, the FDA approved a novel, fine-particle formulation of abiraterone, in combination with methylprednisolone, for the treatment of patients with mCRPC. In studies of healthy males, this formulation at 500 mg was shown to be bioequivalent to 1,000 mg of the originator formulation.^{44,45} In a phase II therapeutic equivalence study, 53 patients with mCRPC who were not treated previously with abiraterone, enzalutamide, radium-223, or chemotherapy (docetaxel for mCRPC completed ≥ 1 year before enrollment was allowed) were randomized to 500 mg daily of the new, fine-particle formulation plus 4 mg methylprednisolone orally twice daily or to 1,000 mg of the originator formulation daily plus 5 mg prednisone orally twice daily.⁴⁶ Bioequivalence of these doses was confirmed based on serum testosterone levels, PSA response, and abiraterone pharmacokinetics. The rates of total and grade 3/4 adverse events were similar between the arms, with musculoskeletal and connective tissue disorders occurring more frequently in the originator-treated patients (37.9% vs 12.5%). The panel believes that the fine-particle formulation of abiraterone can be used instead of the original formulation of abiraterone in the treatment of patients with mCRPC (category 2A).

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- Relugolix has not been adequately studied in combination with potent androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, or abiraterone acetate, nor has it been studied in combination with docetaxel or cabazitaxel chemotherapy. Potential drug interactions include induction of cytochrome P450 enzymes and reduced concentration and efficacy of relugolix with enzalutamide or apalutamide and cardiac QTc interactions with abiraterone. Further studies of relugolix dosing and drug interactions with commonly used agents in advanced prostate cancer are needed to ensure patient safety and proper dosing.
- Data are limited on long-term compliance of oral relugolix and the potential effects on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if patient compliance is uncertain.

Monitor/Surveillance

- ADT has a variety of adverse effects, including hot flashes, loss of libido, erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, anemia, breast enlargement and tenderness/soreness, depression and mood swings, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. The intensity and spectrum of these side effects vary greatly, and many are reversible or can be avoided or mitigated. For example, physical activity can counter many of these symptoms and should be recommended (see NCCN Guidelines for Survivorship[†]). Use of statins also should be considered. Patients and their medical providers should be advised about these risks prior to treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for: 1) calcium (1000–1200 mg daily from food and supplements) and vitamin D3 (400–1000 IU daily); and 2) additional treatment for males aged ≥50 years with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by dual-energy x-ray absorptiometry (DEXA) scan and a 10-year probability of hip fracture ≥3% or a 10-year probability of a

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Based on the studies described here, abiraterone is a category 1, preferred option for mCRPC without prior novel hormone therapy. For patients with mCRPC and prior novel hormone therapy, abiraterone is included in the “other recommended regimens” category. The fine-particle formulation of abiraterone is included under “other recommended options” in all mCRPC settings.

Abiraterone should be given with concurrent steroid (either oral prednisone 5 mg twice daily or oral methylprednisolone 4 mg twice daily, depending on which formulation is given) to abrogate signs of mineralocorticoid excess that can result from treatment. These signs include hypertension, hypokalemia, and peripheral edema. Thus, monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis is warranted during abiraterone therapy. Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

A randomized phase II noninferiority study of 75 patients with M1 CRPC compared 1,000 mg/day abiraterone after an overnight fast with 250 mg/day after a low-fat breakfast.¹⁷ The primary endpoint was log change in PSA, with secondary endpoints of PSA response (≥50%) and PFS. The primary endpoint favored the low-dose arm (log change in PSA, -1.59 vs -1.19), as did the PSA response rate (58% vs 50%), with an

major osteoporosis-related fracture ≥20%. Fracture risk can be assessed using FRAX, the algorithm released by WHO. ADT should be considered “secondary osteoporosis” when using the FRAX algorithm. Treatment options to increase bone density, a surrogate for fracture risk in patients without metastases, include denosumab (60 mg SQ every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly). A baseline DEXA scan should be obtained before starting therapy in patients at increased risk for fracture based on FRAX screening. A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended. The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.

- Denosumab (60 mg SQ every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in patients receiving ADT. These medical conditions are common in older individuals and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in patients receiving ADT should differ from the general population.

equal PFS of 9 months in both arms. Noninferiority of the low dose was established according to the predefined criteria. Therefore, abiraterone can be given at 250 mg/day administered following a low-fat breakfast, as an alternative to the dose of 1,000 mg/day after an overnight fast in patients who will not take or cannot afford the standard dose. The cost savings may reduce financial toxicity and improve adherence. Food impacts absorption unpredictably; side effects should be monitored, and standard dosing (1,000 mg on empty stomach) used if excess toxicity is observed on modified dosing (250 mg with food).

Abiraterone With Dexamethasone in M1 CRPC

Switching from prednisone to dexamethasone 1 mg/day can be considered for patients with M1 CRPC with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy.

The SWITCH study was a single-arm, open-label, phase II study of this approach with 26 enrolled patients.⁴⁷ The primary endpoint, the proportion of patients with a PSA decline ≥30% in 6 weeks, was 46.2%. No significant toxicities were observed, and 2 radiologic responses were seen. In another study, 48 consecutive patients with mCRPC, with disease progression on

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Non-Hormonal Systemic Therapy for M1 Castration-Sensitive Prostate Cancer

- Patients with high-volume castration-sensitive metastatic prostate cancer who are fit for chemotherapy should be considered for ADT plus docetaxel and either abiraterone or darolutamide based on phase 3 studies:
 - ADT plus docetaxel and abiraterone improved overall survival and rPFS in the open-label PEACE-1 study. A modest increase in toxicity was seen.
 - ADT plus docetaxel and darolutamide improved overall survival in the ARASENS trial. Adverse events were similar between arms.
 - The use of myeloid growth factors should follow the NCCN Guidelines for Hematopoietic Growth Factors[†], based on risk of neutropenic fever.

Non-Hormonal Systemic Therapy for M1 CRPC**Chemotherapy**

- Docetaxel with concurrent steroid
 - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Cabazitaxel with concurrent steroid
 - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Cabazitaxel/carboplatin with concurrent steroid
 - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Mitoxantrone with prednisone
 - Every 3-week docetaxel with concurrent steroid is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for patients with symptomatic mCRPC. Radical-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Abiraterone and enzalutamide have been shown to extend survival in patients whose cancer progressed on docetaxel. (See PROS-J). Mitoxantrone with prednisone may provide palliation but has not been shown to extend survival.
- Only regimens utilizing docetaxel on an every-3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.

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abiraterone with prednisone, were switched to abiraterone with 0.5 mg/day dexamethasone.⁴⁸ The primary endpoint of median PFS was 10.35 months, and PSA levels decreased or stabilized in 56% of patients after switching to dexamethasone.

Enzalutamide in M0 and M1 CRPC

In August 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of patients with mCRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase III, placebo-controlled AFFIRM trial.^{49,50} AFFIRM randomized 1,199 patients to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was OS. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63; $P < .001$). Survival was improved in all subgroups analyzed. Secondary endpoints also were improved significantly, which included the proportion of patients with >50% PSA decline (54% vs 2%), radiographic response (29% vs 4%), radiographic PFS (8.3 vs 2.9 months), and time to first skeletal-related event (SRE) (16.7 vs 13.3 months). QOL measured using validated surveys was improved with enzalutamide compared with placebo. Adverse events were mild, and included fatigue (34% vs 29%), diarrhea (21% vs 18%), hot flushes (20% vs 10%), headache (12% vs 6%), and

- Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m² (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel.
- Increasing PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong overall survival, PFS, PSA response, and radiologic response when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Toxicity at this dose was significant and included febrile neutropenia, severe diarrhea, fatigue, nausea/vomiting, anemia, thrombocytopenia, sepsis, and renal failure. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m² every 3 weeks to 20 mg/m² every 3 weeks. Cabazitaxel 20 mg/m² had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m² had a significantly lower PSA response rate but non-significantly lower radiographic response rate and non-significantly shorter PFS and overall survival (13.4 months vs. 14.5 months) compared to 25 mg/m². Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for patients with mCRPC whose cancer has progressed despite prior docetaxel chemotherapy. Cabazitaxel 25 mg/m² with concurrent steroid may be considered for healthy patients who wish to be more aggressive. Growth factor support may be needed with either dose.
- Cabazitaxel at 25 mg/m² with concurrent steroid improved rPFS and reduced the risk of death compared with abiraterone or enzalutamide in patients with prior docetaxel treatment for mCRPC in the CARD study.
- Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, TP53, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

seizures (0.6% vs 0%). The incidence of cardiac disorders did not differ between the arms. Enzalutamide is dosed at 160 mg daily. Patients in the AFFIRM study were maintained on LHRH agonist/antagonist therapy and could receive bone supportive care medications. The seizure risk in the enzalutamide FDA label was 0.9% versus 0.6% in the manuscript.^{49,51}

Another phase III trial studied enzalutamide in the prechemotherapy setting. The PREVAIL study randomly assigned 1,717 patients with chemotherapy-naïve metastatic prostate cancer to daily enzalutamide or placebo.^{52,53} The study was stopped early due to benefits shown in the treatment arm. Compared with the placebo group, the enzalutamide group showed improved median PFS (20.0 vs 5.4 months) and median OS (35.3 vs 31.3 months). Improvements in all secondary endpoints were also observed (eg, the time until chemotherapy initiation or first SRE).

Two randomized clinical trials have reported that enzalutamide may be superior to bicalutamide for cancer control in mCRPC. The TERRAIN study randomized 375 patients with treatment-naïve, mCRPC to 160 mg/day enzalutamide or 50 mg/day bicalutamide in a 1:1 manner.⁵⁴ The enzalutamide group had significantly better PFS (defined as PSA progression, soft tissue progression, or development of additional bony metastases) compared

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

- Docetaxel retreatment can be attempted after progression on a novel hormone therapy in patients with metastatic CRPC whose cancer has not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-sensitive setting.
- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged.
- Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
- No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens. See NCCN Guidelines for Hematopoietic Growth Factors[†] for recommendations on growth factor support.

Targeted Therapy

- Consider inclusion of olaparib in patients who have an *HRR* mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy. Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) who have been treated previously with androgen receptor-directed therapy. However, efficacy appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis. There may be heterogeneity of response to olaparib for non-*BRCA* mutations based on which gene has the specific gene mutation.
- Consider inclusion of rucaparib for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.
- Olaparib with abiraterone is an option for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy and who have not yet had treatment in the setting of metastatic CRPC.
- Talazoparib plus enzalutamide is a treatment option for patients with

metastatic CRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC, depending on prior treatment in other disease settings (see PROS-15). There may be heterogeneity of response based on the specific gene mutation. (See Discussion). Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

- Niraparib plus abiraterone (combination tablet) is a treatment option for patients with metastatic CRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of metastatic CRPC, depending on prior treatment in other disease settings (see PROS-15). Use of niraparib/abiraterone for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Immunotherapy

- Patients with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.
- Sipuleucel-T
 - Sipuleucel-T is only for asymptomatic or minimally symptomatic patients with no liver metastases, life expectancy >6 months, and ECOG performance status 0–1.
 - Sipuleucel-T is not recommended for patients with small cell/NEPC.
 - Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 months in the control arm to 25.8 months in the treatment arm, which constitutes a 22% reduction in mortality risk.
 - Sipuleucel-T is well-tolerated; common complications include chills, pyrexia, and headache.
- Pembrolizumab (for MSI-H, dMMR, or TMB ≥10 mut/Mb)
 - Pembrolizumab is recommended only as subsequent systemic therapy for patients with metastatic CRPC whose cancer has progressed through prior docetaxel and a novel hormone therapy.

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with the bicalutamide group (median time to progression, 15.7 vs 5.8 months; HR, 0.44; 95% CI, 0.34–0.57).

The STRIVE trial randomized 396 patients with M0 or M1 treatment-naïve CRPC to 160 mg/day enzalutamide or 50 mg/day bicalutamide in a 1:1 manner.⁵⁵ The primary endpoint in this study was PFS, defined as either PSA progression, radiographic progression of disease, or death from any cause. Enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (HR, 0.24; 95% CI, 0.18–0.32). These studies demonstrated that enzalutamide extended PFS better than bicalutamide in patients choosing an antiandrogen for secondary hormonal therapy treatment of CRPC. Bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.

Thus, enzalutamide represents a category 1, preferred treatment option for patients without prior novel hormone therapy in the mCRPC setting. For patients with mCRPC and prior novel hormone therapy, enzalutamide is included in the “other recommended regimens” group of options.

The randomized, double-blind, placebo-controlled phase III PROSPER trial assessed the use of enzalutamide in 1,401 patients with nonmetastatic CRPC.⁵⁶ Patients with PSADT ≤10 months were stratified according to PSADT (<6 months vs ≥6 months) and use of bone-sparing agents and randomized 2:1 to enzalutamide (160 mg/d)

plus ADT or placebo plus ADT. Enzalutamide improved the primary endpoint of metastasis-free survival over placebo (36.6 vs 14.7 months; HR for metastasis or death, 0.29; 95% CI, 0.24–0.35; $P<.0001$). Median OS was longer in the enzalutamide group than in the placebo group (67.0 vs 56.3 months; HR for death, 0.73; 95% CI, 0.61–0.89; $P=.001$).⁵⁷ Adverse events included fatigue (33% vs 14%), hypertension (12% vs 5%), major adverse cardiovascular events (5% vs 3%), and mental impairment disorders (5% vs 2%). Patient-reported outcomes from PROSPER indicate that enzalutamide delayed pain progression, symptom worsening, and decrease in functional status, compared with placebo.⁵⁸

The FDA expanded approval for enzalutamide to include patients with nonmetastatic CRPC in July 2018, and the panel believes that patients with M0 CRPC can be offered enzalutamide, if PSADT is ≤10 months (category 1, preferred option).

Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.⁴⁹

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with nonmetastatic CRPC in February 2018. This approval was based on the phase III SPARTAN trial of 1,207 patients with M0 CRPC and PSADT ≤10 months.⁵⁹ Participants were

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Prevention of Skeletal-Related Events

- In patients with CRPC who have bone metastases, denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or RT to bone.
- When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal-related events.
- A phase 3 clinical trial that assessed a role for zoledronic acid in patients beginning ADT for bone metastases was negative.
- Choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.
 - Denosumab (preferred) is given SQ every 4 weeks. Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance <30 mL/min. When creatinine clearance is <60 mL/min, the risk for severe hypocalcemia increases. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels.
 - Zoledronic acid is given IV every 3 to 4 weeks or every 12 weeks. The dose is based on the serum creatinine obtained just prior to each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance <30 mL/min.
- Osteonecrosis of the jaw (ONJ) is seen with both agents; risk is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. Patients should be referred for dental evaluation before starting either zoledronic acid or denosumab. If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s).
- The optimal duration of therapy for either denosumab or zoledronic acid remains uncertain.
- The toxicity profile of denosumab when denosumab is used in patients who have been treated with zoledronic acid remains uncertain.

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stratified according to PSADT (>6 months vs ≤6 months), use of bone-sparing agents, and the presence of metastatic pelvic lymph nodes (N0 vs N1). After a median follow-up of 20.3 months, apalutamide at 240 mg/day with ADT improved the primary endpoint of metastasis-free survival over placebo with ADT (40.5 vs 16.2 months; HR for metastasis or death, 0.28; 95% CI, 0.23–0.35; $P<.001$). Adverse events included rash (24% vs 5.5%), fracture (11% vs 6.5%), and hypothyroidism (8% vs 2%). In a prespecified exploratory analysis of SPARTAN, health-related QOL was maintained in both the apalutamide and placebo groups.⁶⁰

After a median follow-up of 52 months, final OS analysis showed that participants in SPARTAN experienced an improved median OS with apalutamide versus placebo (73.9 vs 59.9 months; HR, 0.78; 95% CI, 0.64–0.96; $P=.016$).⁶¹ This longer OS reached prespecified statistical significance, even though 19% of participants crossed over from placebo to apalutamide.

Apalutamide is a category 1, preferred option for patients with M0 CRPC if PSADT is ≤10 months.

Darolutamide in M0 CRPC

The FDA approved darolutamide for treatment of patients with nonmetastatic CRPC in July 2019. The phase III ARAMIS study randomized 1,509 patients with M0 CRPC and PSADT ≤10 months 2:1 to darolutamide

(600 mg twice daily) or placebo.⁶² Participants were stratified according to PSADT (>6 vs ≤6 months) and the use of osteoclast-targeted agents. The median follow-up time was 17.9 months. Darolutamide improved the primary endpoint of metastasis-free survival compared with placebo (40.4 vs 18.4 months; HR for metastasis or death, 0.41; 95% CI, 0.34–0.50; $P<.001$).

Patients in the placebo group of ARAMIS crossed over to darolutamide ($n=170$) or received other life-prolonging therapy ($n=137$). Final analysis occurred after a median follow-up time of 29.0 months. The risk of death was 31% lower in the darolutamide group than in the placebo group (HR for death, 0.69; 95% CI, 0.53–0.88; $P=.003$).⁶³ OS at 3 years was 83% (95% CI, 80–86) in the darolutamide group compared with 77% (95% CI, 72–81) in the placebo group. Adverse events that occurred more frequently in the treatment arm included fatigue (12.1% vs 8.7%), pain in an extremity (5.8% vs 3.2%), and rash (2.9% vs 0.9%). The incidence of fractures was similar between darolutamide and placebo (4.2% vs 3.6%).⁶²

Darolutamide is a category 1, preferred option for patients with M0 CRPC if PSADT is ≤10 months.

Other Secondary Hormone Therapies

Other options for secondary hormone therapy include a first-generation antiandrogen, antiandrogen withdrawal,

corticosteroid, or ketoconazole (adrenal enzyme inhibitor) with hydrocortisone.^{64–66} However, none of these strategies has yet been shown to prolong survival in randomized clinical trials.

A randomized phase II trial, TRANSFORMER, compared the effect of bipolar androgen therapy (BAT) with that of enzalutamide on PFS in 195 patients with asymptomatic, metastatic CRPC (mCRPC) with prior progression on abiraterone.⁶⁷ BAT involves rapid cycling between high and low serum testosterone to disrupt the adaptive upregulation of the androgen receptor that occurs with low testosterone levels. Patients in the BAT arm received testosterone cypionate 400 mg intramuscularly once every 28 days. The PFS was 5.7 months in both arms (HR, 1.14; 95% CI, 0.83–1.55; $P=.42$). Cross-over was allowed after disease progression, and OS was similar between the groups. BAT resulted in more favorable patient-reported QOL. The Panel awaits more data on this approach.

Chemotherapy, Immunotherapy, and Targeted Therapy for mCRPC

Research has expanded the therapeutic options for patients with mCRPC. In addition to the hormonal and radiopharmaceutical therapies described in other sections, options include chemotherapy, immunotherapy, targeted therapy. As noted previously, selection of therapy depends on patient preferences, prior treatment exposures, the presence or absence of symptoms, the location of metastases, the presence of certain biomarkers, and consideration of potential side effects.

Docetaxel

Two randomized phase III studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive CRPC (TAX 327 and SWOG 9916).^{68–70} TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1,006 patients.⁶⁹ Every-3-week docetaxel resulted in higher median OS than mitoxantrone (18.9 vs 16.5 months; $P=.009$). This survival benefit was maintained at extended follow-up.⁷⁰ The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared with mitoxantrone plus prednisone.⁶⁸

Docetaxel is FDA-approved for mCRPC. The standard regimen is every 3 weeks. An alternative to every-3-week docetaxel is a biweekly regimen of 50 mg/m². This regimen is based on a large randomized phase II trial of 346 patients with mCRPC randomized to either every-2-week docetaxel or every-3-week docetaxel, each with maintenance of ADT and prednisone.⁷¹ Patients treated with the every-2-week regimen survived an average of 19.5 months compared with 17.0 months with the

every-3-week regimen ($P=.015$). Time-to-progression and PSA decline rate favored every-2-week therapy. Tolerability was improved with every-2-week docetaxel; the febrile neutropenia rate was 4% versus 14%, and other toxicities and overall QOL were similar.

Treatment with 8 or more cycles of docetaxel may be associated with better OS than fewer cycles in the mCRPC setting, but prospective trials are necessary to test 6 versus 10 cycles of docetaxel in the metastatic castration-sensitive and CRPC settings.⁷² Retrospective analysis from the GETUG-AFU 15 trial suggests that docetaxel only benefits some patients with CRPC who received docetaxel in the castration-sensitive setting.⁷³

Thus, docetaxel is a category 1 preferred option for treatment of docetaxel-naïve mCRPC. The panel believes that docetaxel can be given as a rechallenge after progression on a novel hormone in the mCRPC setting if given in the castration-sensitive setting.

The NCCN panel agreed that docetaxel rechallenge may be useful in some patients (category 2A instead of category 1 in this setting), especially in those who have not shown definitive evidence of progression on prior docetaxel therapy. Docetaxel rechallenge can be considered in patients who received docetaxel with ADT in the metastatic castration-sensitive setting.

Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semisynthetic taxane derivative, for patients with mCRPC previously treated with a docetaxel-containing regimen. An international randomized phase III trial (TROPIC) randomized 755 patients with progressive mCRPC to receive cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m², each with daily prednisone.⁷⁴ A 2.4-month improvement in OS was demonstrated with cabazitaxel compared with mitoxantrone (HR, 0.72; $P<.0001$). The improvement in survival was balanced against a higher toxic death rate with cabazitaxel (4.9% vs 1.9%), which was due, in large part, to differences in rates of sepsis and renal failure. Febrile neutropenia was observed in 7.5% of cabazitaxel-treated patients versus 1.3% of mitoxantrone-treated patients. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated patients, which indicated the need for vigilance and treatment or prophylaxis in this setting to prevent febrile neutropenia. The survival benefit was sustained at an updated analysis with a median follow-up of 25.5 months.⁷⁵ Furthermore, results of a posthoc analysis of this trial suggested that the occurrence of grade ≥ 3 neutropenia after cabazitaxel treatment was associated with improvements in both PFS and OS.⁷⁶

The multicenter CARD study was a randomized, open-label clinical trial that compared cabazitaxel with

either abiraterone or enzalutamide in 255 patients with mCRPC who had previously received docetaxel and either abiraterone or enzalutamide.⁷⁷ Cabazitaxel at 25 mg/m² with concurrent steroid improved the primary endpoint of radiographic PFS (8.0 vs 3.7 months; HR, 0.54; $P<.0001$) and reduced the risk of death (13.6 vs 11.0 months; HR, 0.64; $P=.008$) compared with abiraterone or enzalutamide in these patients. Cabazitaxel was also associated with an increased rate of pain response and delayed time to pain progression and SREs.⁷⁸

The phase III open-label, multinational, noninferiority PROSELICA study compared 20 mg/m² cabazitaxel with 25 mg/m² cabazitaxel in 1,200 patients with mCRPC who experienced progression on docetaxel.⁷⁹ The lower dose was found to be noninferior to the higher dose for median OS (13.4 months [95% CI, 12.19–14.88] vs 14.5 months [95% CI, 13.47–15.28]), and grade 3–4 adverse events were decreased (39.7% vs 54.5%). In particular, grade ≥ 3 neutropenia rates were 41.8% and 73.3% for the lower and higher dose groups, respectively.

Results from the phase III FIRSTANA study suggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.⁸⁰ Median OS, the primary endpoint, was similar between 20 mg/m² cabazitaxel, 25 mg/m² cabazitaxel, and 75 mg/m² docetaxel (24.5 months, 25.2 months, and 24.3 months, respectively). Cabazitaxel was associated with lower rates of peripheral sensory neuropathy than docetaxel, particularly at 20 mg/m² (12% vs 25%). However, the panel does not currently recommend cabazitaxel in docetaxel-naïve patients.

Based on these data, cabazitaxel is included in these NCCN Guidelines as a preferred option after progression occurs on docetaxel in patients with mCRPC (category 1 after progression on docetaxel and a novel hormone therapy). Cabazitaxel at 20 mg/m² every 3 weeks, with or without growth factor support, is the recommended dose for fit patients. Cabazitaxel at 25 mg/m² may be considered for healthy patients who wish to be more aggressive.

Cabazitaxel should be given with concurrent steroids (daily prednisone or dexamethasone on the day of chemotherapy). Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pretreated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis) and symptom-directed antidiarrheal agents. Cabazitaxel was tested in patients with hepatic dysfunction in a small, phase I, dose-escalation study.⁸¹ Cabazitaxel was tolerated in patients with mild to moderate hepatic impairment. However, cabazitaxel should not be used in patients with severe hepatic dysfunction. Cabazitaxel should be stopped upon clinical disease progression or intolerance.

Cabazitaxel/Carboplatin

Cabazitaxel 20 mg/m² plus carboplatin area under the curve 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant mCRPC (visceral metastases, low PSA and bulky disease, high lactate dehydrogenase, high carcinoembryonic antigen, lytic bone metastases, neuroendocrine prostate cancer histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RBI*). This recommendation is based on a phase I-II, open label, randomized study.⁸² In the phase II portion, 160 patients were randomized to receive cabazitaxel alone or with carboplatin, and the primary endpoint was investigator-assessed PFS. In the intention-to-treat population, median PFS was 4.5 months in the cabazitaxel arm versus 7.3 months in the cabazitaxel/carboplatin arm (HR, 0.69; 95% CI, 0.50–0.95; $P=.018$). The most common grade 3–5 adverse events (fatigue, anemia, neutropenia, and thrombocytopenia) were all more common in the combination arm. Posthoc analyses showed that patients with aggressive variant disease had a longer median PFS in the combination arm than the cabazitaxel arm (7.5 vs 1.7 months; $P=.017$). Patients without aggressive variant tumors, conversely, had similar median PFS regardless of treatment (6.5 vs 6.3 months; $P=.38$).

Sipuleucel-T

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. This autologous cancer “vaccine” involves collection of the white blood cell fraction-containing, antigen-presenting cells from each patient; exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein); and subsequent reinfusion of the cells. The pivotal study was a phase III, multicenter, randomized, double-blind trial (D9902B).⁸³ Five hundred twelve patients with minimally symptomatic or asymptomatic mCRPC were randomized 2:1 to receive sipuleucel-T or placebo. Of patients, 18.2% had received prior chemotherapy, which included docetaxel; eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month prior to enrollment. Median survival in the vaccine arm was 25.8 months compared with 21.7 months in the control arm. In a subset analysis, both those who did and those who did not receive prior chemotherapy benefited from sipuleucel-T treatment. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk (HR, 0.78; 95% CI, 0.61–0.98; $P=.03$). Common complications included mild to moderate chills (54.1%), pyrexia (29.3%), and headache (16.0%), which usually were transient.

A prospective registry of patients with mCRPC, PROCEED, enrolled 1,976 patients from 2011 to 2017,

who were followed for a median of 46.6 months.⁸⁴ The safety and tolerability of sipuleucel-T were consistent with previous findings, and the median OS was 30.7 months (95% CI, 28.6–32.2 months).

Sipuleucel-T is a category 1 option for certain patients with mCRPC who have not had previous treatment with docetaxel or with a novel hormone therapy. Benefit of sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T is also not recommended for patients with small cell/neuroendocrine prostate cancer. The panel prefers that sipuleucel-T be used as a therapy for asymptomatic or minimally symptomatic patients with mCRPC, so that disease burden is lower and immune function is potentially more intact. However, it is also an option for patients with mCRPC who have had prior treatment with docetaxel or a novel hormone therapy, but not for patients who have already received both. Patients should have good performance level (ECOG 0–1), estimated life expectancy >6 months, and no liver metastases. Clinicians and patients should be aware that the usual markers of benefit (decline in PSA and improvement in bone or CT scans) are not seen. Therefore, benefit to the individual patient cannot be ascertained using currently available testing.

Treatment after sipuleucel-T treatment should proceed as clinically indicated, particularly if symptoms develop.

Pembrolizumab

The FDA approved the use of pembrolizumab, an anti-PD1 antibody, for treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors who have progressed on prior treatment and who have no satisfactory alternative treatment options in May 2017. This approval was based on the treatment of 149 patients across 5 clinical studies involving MSI-H or dMMR colorectal (n=90) or noncolorectal (n=59) cancer for an objective response rate of 40% (59/149).⁵¹ All patients received 1 or more prior regimen. Among the noncolorectal cohorts, 2 patients had mCRPC: one experienced a partial objective response, and the other experienced stable disease for more than 9 months.

Outcomes of additional patients with mCRPC treated with pembrolizumab have been reported.^{85–90} In an early study, 10 patients with CRPC and nonvisceral metastases (bone = 7; lymph nodes = 2; bone and liver = 1) who had disease progression on enzalutamide were treated with pembrolizumab and enzalutamide.⁸⁵ Some of the patients also had experienced disease progression on additional therapies (docetaxel for castration-sensitive disease, abiraterone, and/or sipuleucel-T). Three of the 10 patients showed a near complete PSA response. Two of these 3 patients had radiographically measurable

disease and experienced a partial radiographic response (including a response in liver metastases). Of the remaining patients, 3 showed stable disease, and 4 showed no evidence of clinical benefit. Genetic analysis of biopsy tissue revealed that one patient whose disease showed PSA response had an MSI-H tumor, whereas the other patient with responsive disease and two with nonresponsive disease did not. The nonrandomized phase Ib KEYNOTE-028 trial included 23 patients with advanced, progressive prostate cancer, of whom 74% had received 2 or more previous therapies for metastatic disease.⁸⁷ The objective response rate by investigator review was 17.4% (95% CI, 5.0%–38.8%), with 4 confirmed partial responses. Eight patients (34.8%) had stable disease. Treatment-related adverse events occurred in 61% of patients after a median follow-up of 7.9 months; 17% of the cohort experienced grade 3–4 events (ie, grade 4 lipase increase, grade 3 peripheral neuropathy, grade 3 asthenia, grade 3 fatigue).

KEYNOTE-199 was a multicohort, open-label phase II study in 258 patients with mCRPC and prior treatment with docetaxel and at least one novel hormonal therapy that assessed pembrolizumab in patients regardless of MSI status.⁹¹ Cohorts 1 and 2 included patients with PD-L1-positive (n=133) and PD-L1-negative (n=66) prostate cancer, respectively. Cohort 3 included those with bone-predominant disease with positive or negative PD-L1 expression (n=59). The primary endpoint of overall response rate was 5% (95% CI, 2%–11%) in cohort 1 and 3% (95% CI, <1%–11%) in cohort 2. Responses were durable (range, 1.9 – ≥21.8 months).

The most common adverse events from pembrolizumab are fatigue, pruritus, diarrhea, anorexia, constipation, nausea, rash, fever, cough, dyspnea, and musculoskeletal pain. Pembrolizumab also may be associated with immune-mediated side effects, which include colitis, hepatitis, endocrinopathies, pneumonitis, or nephritis.

Based on the available data, the panel supports the use of pembrolizumab in patients with MSI-H or dMMR mCRPC whose disease has progressed through docetaxel and a novel hormone therapy. The prevalence of MMR deficiency in metastatic CRPC is estimated at 2%–5%,^{86,92} and testing for MSI-H or dMMR can be performed using DNA testing or immunohistochemistry. If tumor MSI-H or dMMR is identified, the panel recommends referral to genetic counseling for consideration of germline testing for Lynch syndrome.

In June 2020, the FDA granted accelerated approval for pembrolizumab's use in patients with unresectable or metastatic TMB-high (TMB-H) (≥ 10 mutations/megabase [mut/Mb]) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Results from prospective biomarker analysis of the multicohort, nonrandomized, open-label,

phase II KEYNOTE-158 trial support this approval.⁹³ The prospective TMB study included an efficacy population of 790 patients with anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, or vulvar cancer who were evaluable for TMB. Of these, 102 patients (13%) had TMB-H status. Objective responses to pembrolizumab were seen in 30 of 102 patients in the TMB-H group (29%; 95% CI, 21%–39%) and 43 of 688 patients in the non-TMB-H group (6%; 95% CI, 5%–8%). Safety was as expected based on other studies of pembrolizumab. Even though there were no patients with prostate cancer in the TMB pembrolizumab study, the panel includes pembrolizumab as an option for patients with mCRPC, prior docetaxel and novel hormone therapy, and TMB ≥ 10 mut/Mb based on extrapolation from other tumor types.

Mitoxantrone

Two randomized trials assessed the role of mitoxantrone in patients with mCRPC.^{94,95} Although there was no improvement in OS, palliative responses and improvements in QOL were seen with mitoxantrone.

Mitoxantrone can be used for palliation in symptomatic patients with mCRPC who cannot tolerate other therapies after disease progression on prior docetaxel.

Treatment Options for Patients With DNA Repair Gene Mutations

Early studies suggest germline and somatic mutations in HRR genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.^{96–98} PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.⁹⁹ PARP inhibitor therapy options are discussed subsequently.

DNA repair defects have also been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.^{100–104} Platinum agents have shown some activity in patients with CRPC without molecular selection.¹⁰⁵ Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

In addition, results of one study suggested that patients with mCRPC and germline mutations in DNA repair genes may have better outcomes if treated with abiraterone or enzalutamide than with taxanes.¹⁰⁶ However, it should be noted that the response of patients with mCRPC and HRR gene mutations (HRRm) to standard therapies is similar to the response of patients without mutations.^{107,108}

Patients with *CDK12* mutations tend to have aggressive disease with high rates of metastases and short OS. Their disease also does not respond well to hormonal therapy, PARP inhibitors, or taxanes. Two large, multi-institutional, retrospective studies have shown that 11% to

33% of patients with mCRPC and *CDK12* mutations experienced disease response to PD-1 inhibitors (ie, nivolumab, pembrolizumab), some with durable responses.^{109,110} The panel awaits more data on the use of PD-1 inhibition in patients with *CDK12* mutations.

Olaparib

Preliminary clinical data using olaparib suggested favorable activity of this agent in patients with HRRm, but not in those without HRRm.^{97,98,111} The phase III PROfound study was a randomized trial evaluating olaparib 300 mg twice daily versus physician's choice of abiraterone or enzalutamide in patients with mCRPC and progression on at least one novel hormonal agent (abiraterone or enzalutamide) and up to one prior taxane agent (permitted but not required).¹¹² Patients were required to have a somatic or germline HRRm, and were allocated to one of two cohorts: cohort A comprised patients with *BRCA1/2* or *ATM* mutations, and cohort B comprised patients with a mutation in at least 1 of 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*). The primary endpoint of improving radiographic PFS with olaparib versus abiraterone/enzalutamide was met in cohort A (HR, 0.34; 95% CI, 0.25–0.47; $P < .001$), and radiographic PFS was also superior in the entire study population encompassing cohorts A+B (HR, 0.49; 95% CI, 0.38–0.63; $P < .001$).

In addition, final OS analysis of PROfound showed that OS was improved with olaparib versus abiraterone/enzalutamide in cohort A (HR, 0.69; 95% CI, 0.50–0.97; $P = .02$), despite the fact that 86 of 131 patients (66%) crossed over to olaparib after disease progression in the control arm.¹¹³

The panel notes that there may be heterogeneity of response to olaparib based on which gene has a mutation. Efficacy in PROfound appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis.¹¹³ Patients with *BRCA2* mutations in PROfound experienced an OS benefit with olaparib (HR, 0.59; 95% CI, 0.37–0.95), whereas the HR for OS in patients with *ATM* mutations was 0.93 (95% CI, 0.53–1.75).¹¹³ Furthermore, there were few patients in PROfound with mutations in some of the genes. For example, only 4 patients had *BRIP1* mutations (2 in olaparib arm and 2 in control arm), 2 patients had *RAD51D* mutations (both in olaparib arm), and no patients had *RAD51C* mutations.¹¹² Patients with *PPP2R2A* mutations in PROfound experienced an unfavorable risk-benefit profile.

As a result of the favorable efficacy data from the PROfound trial, the FDA approved olaparib (300 mg twice daily) in May 2020 for use in patients with mCRPC

and deleterious or suspected deleterious germline or somatic HRRm in at least one of 14 genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) and who had previously received treatment with enzalutamide or abiraterone.

Because prior taxane therapy was not mandated in the PROfound study, olaparib use might be reasonable in mCRPC patients before or after docetaxel treatment. Adverse events that may occur with olaparib treatment include anemia (including that requiring transfusion), fatigue, nausea or vomiting, anorexia, weight loss, diarrhea, thrombocytopenia, creatinine elevation, cough, and dyspnea. Rare but serious side effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonitis, and a theoretical risk of myelodysplasia or acute myeloid leukemia.¹¹²

The panel recommends olaparib as an option for patients with mCRPC, previous androgen receptor-directed therapy, and an HRRm regardless of prior docetaxel therapy (category 1). The HRR genes to be considered for use of olaparib are *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*.

Any commercially available analytically and clinically validated somatic tumor and ctDNA assays and germline assays can be used to identify patients for treatment. Careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during olaparib therapy.

Rucaparib

Rucaparib is another PARP inhibitor approved for use in patients with mCRPC. This agent received accelerated FDA approval in May 2020 based on the preliminary favorable data from the TRITON2 clinical trial. In that open-label, single-arm phase II trial, patients with mCRPC harboring a deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutation, who had previously received therapy with a novel hormonal agent plus one taxane chemotherapy, were treated with rucaparib 600 mg twice daily.¹¹⁴ The primary endpoint of TRITON2 was the objective response rate in patients with measurable disease; it was 43.5% (95% CI, 31.0%–56.7%) in this population with *BRCA1/2*-mutations. Median radiographic PFS, a key secondary endpoint, was 9.0 months (95% CI, 8.3–13.5 months). The most common adverse events were asthenia/fatigue, nausea, and anemia/decreased hemoglobin, with grade ≥ 3 anemia/decreased hemoglobin in 25.2% of participants. Final analysis of TRITON2 confirmed results of the earlier analysis.¹¹⁵

In the randomized phase III TRITON3 study, patients with mCRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who have previously received a novel hormonal agent but no chemotherapy for mCRPC were randomized 2:1 to rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel).¹¹⁶ The primary endpoint of TRITON3, the median duration of imaging-based PFS, was significantly longer at 62 months in the group of 270 participants assigned to receive rucaparib than in the 135 participants who received a control medication (10.2 vs 6.4 months; HR, 0.61; 95% CI, 0.47–0.80; $P < .001$). This effect was also seen in the 201 patients and 101 patients in each group with a *BRCA* mutation (11.2 vs 6.4 months; HR, 0.50; 95% CI, 0.36–0.69). For those with *ATM* mutations, an exploratory analysis suggested a possible improvement as well (8.1 vs 6.8 month; HR, 0.95; 95% CI, 0.59–1.52). As in TRITON2, the most frequent adverse events with rucaparib were fatigue and nausea.

The panel recommends rucaparib as an option for patients with mCRPC, prior treatment with a novel hormone therapy, and a *BRCA1* or *BRCA2* mutation. Rucaparib should not be used in patients with HRRm other than *BRCA1/2*.¹¹⁷ Adverse events that may occur with rucaparib include anemia (including that requiring transfusion), fatigue, asthenia, nausea or vomiting, anorexia, weight loss, diarrhea or constipation, thrombocytopenia, increased creatinine, increased liver transaminases, and rash. Rare but serious side effects of rucaparib include a theoretical risk of myelodysplasia or acute myeloid leukemia, as well as fetal teratogenicity.^{114,117}

The preferred method of selecting patients for rucaparib treatment is somatic analysis of *BRCA1* and *BRCA2* using a ctDNA sample. As with olaparib, careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during treatment with rucaparib.

Olaparib Plus Abiraterone

Preclinical data suggest that PARP-1 promotes androgen receptor activity.¹¹⁸ Additional preclinical data show that androgen receptor inhibitors can downregulate DNA repair genes, creating a situation similar to that of HRRm.^{119,120} These results suggest that the combination of PARP inhibition with androgen receptor inhibition may have an enhanced antitumor effect and that this effect may not be limited to patients with HRRm. In fact, a randomized phase II trial showed that the combination of abiraterone with olaparib increased radiographic PFS over abiraterone and placebo in patients with mCRPC regardless of HRR status (intent to treat [ITT] population: HR, 0.65; 95% CI, 0.44–0.97; $P = .034$).⁹⁸

The PROpel trial was an international, double-blind, phase III trial comparing abiraterone and olaparib with abiraterone and placebo in 796 patients with mCRPC regardless of HRR mutation status.¹²¹ Prior docetaxel in the localized or metastatic castration-sensitive setting was allowed, but patients were untreated for CRPC. The primary end point, imaging-based PFS by investigator assessment in the ITT population, was significantly longer in the abiraterone/olaparib group than in the abiraterone/placebo group (24.8 vs 16.6 months; HR, 0.66; 95% CI, 0.54–0.81; $P<.001$). HRRm were identified in tumors of 226 patients; 552 patients did not have HRR tumor mutations. The HR for the primary endpoint in those with HRRm was 0.50 (95% CI, 0.34–0.73). The safety profile of the olaparib/abiraterone combination was as expected based on the known safety profiles of the individual drugs, with the most common adverse events being anemia, fatigue/asthenia, and nausea.

OS data from PROpel were presented at the 2023 ASCO Genitourinary Cancers Symposium.¹²² A trend toward an OS benefit with the abiraterone/olaparib combination was seen in the ITT population and in the HRRm, non-HRRm, *BRCA* mutation, and non-*BRCA* mutation subgroups. However, crossover was not allowed, so patients with HRRm in the control arm were unable to receive olaparib, likely contributing to the inferior survival in the control group.

In May 2023, the FDA approved the combination of olaparib with abiraterone for the treatment of adult patients with *BRCA* mutation mCRPC. Based on the results of PROpel, olaparib/abiraterone is included in NCCN Guidelines as an option in first line mCRPC for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy or docetaxel (category 1) and for those who received prior docetaxel in the castration-sensitive setting (category 2A).

Talazoparib Plus Enzalutamide

Talazoparib is another PARP inhibitor; it has had an FDA indication in breast cancer. The open-label, international phase II TALAPRO-1 trial included 127 patients with an HRRm and progressive, mCRPC, all of whom received at least one dose of talazoparib.¹²³ The objective response rate after a median follow-up of 16.4 months was 29.8% (95% CI, 21.2–39.6). The most common grade 3–4 treatment-emergent adverse events were anemia (31%), thrombocytopenia (9%), and neutropenia (8%).

As noted previously (see “Olaparib Plus Abiraterone”, page 1086), preclinical data suggest that the PARP inhibition combined with androgen receptor inhibition may have an enhanced antitumor effect that may not be limited to those with HRRm. The randomized, double-blind, phase III TALAPRO-2 study compared

enzalutamide plus talazoparib with enzalutamide plus placebo in 805 patients with untreated mCRPC.¹²⁴ HRR gene alteration status and treatment with docetaxel and/or abiraterone in the castration-sensitive setting were used to stratify the randomization. The primary end point was radiographic PFS in the ITT population. At the planned primary analysis, median radiographic PFS was not reached (95% CI, 27.5 months—not reached) for the talazoparib group and 21.9 months (95% CI, 16.6–25.1) for control group (HR, 0.63; 95% CI, 0.51–0.78; $P<.0001$).

HRRm were present in 21% of TALAPRO-2 participants, with *BRCA* alterations as the most common.¹²⁴ The HR for radiographic PFS in the HRR-deficient subgroup was more strongly in favor of the talazoparib combination than in the HRR-proficient/unknown population (0.46 [95% CI, 0.30–0.70; $P=.0003$] vs 0.70 [95% CI, 0.54–0.89; $P=.0039$]). Among those with HRRm, talazoparib conferred a 77% lower risk of radiographic progression or death in those with tumor mutations in *BRCA1* or *BRCA2* (HR 0.23; 95% CI, 0.10–0.53; $P=.0002$), whereas the corresponding reduction was 34% (HR, 0.66; 95% CI, 0.39–1.12; $P=.12$) in those with non-*BRCA* HRR alterations.

Prior therapy also affected the radiographic PFS outcomes in this trial.¹²⁴ In the 179 participants in TALAPRO-2 who had received docetaxel in earlier disease settings, the HR for radiographic PFS was 0.51 (95% CI, 0.32–0.81; $P=.0034$). In the small population of 50 participants in the ITT population who had received prior novel hormonal therapy, the corresponding HR was nonsignificant at 0.57 (95% CI, 0.28–1.16; $P=.12$).

The safety profile of enzalutamide plus talazoparib was consistent with the known safety profiles of the individual drugs, with the most common adverse events in those who received talazoparib being anemia, neutropenia, and fatigue. However, hematologic adverse events were of higher grades and occurred more frequently than would be expected with talazoparib alone. Overall, the combination had significant toxicity, with dose interruption due to adverse events in 75% of participants in the talazoparib group compared with 23% in the placebo group. Dose reductions due to adverse events occurred in 56% and 7% of the talazoparib and placebo groups, respectively.

Based on these results, the FDA approved talazoparib plus enzalutamide for HRRm mCRPC in June 2023. The panel includes talazoparib plus enzalutamide as a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in one of certain HRR and other DNA repair genes (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC. This is a category 1 recommendation for those without prior docetaxel or prior novel hormone therapy. It is a category 2A recommendation for those

with prior docetaxel in the castration-sensitive setting and no prior novel hormone therapy. Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Niraparib Plus Abiraterone

Another PARP inhibitor, niraparib, has also been studied in combination with androgen inhibition in the setting of mCRPC. The randomized, double-blinded phase III MAGNITUDE trial compared niraparib plus abiraterone to placebo plus abiraterone in 423 patients with mCRPC and HRRm and an additional 247 patients without HRRm.¹²⁵ Prior chemotherapy and novel hormonal therapy was allowed in the metastatic castration-sensitive or M0 CRPC settings, and was received by 3.1% and 20.1% of the total HRRm cohort, respectively.

The primary endpoint of MAGNITUDE was radiographic PFS. After a median follow-up of 18.6 months, radiographic PFS was improved for those receiving niraparib in the HRRm group overall (16.5 versus 13.7 months; HR, 0.73; 95% CI, 0.56–0.96; $P=.022$) as well as in the *BRCA* mutation subgroup (16.6 versus 10.9 months; HR, 0.53; 95% CI, 0.36–0.79; $P=.001$). However, radiographic PFS was not improved in the subgroup of patients with non*BRCA* HRRm (HR, 0.99; 95% CI, 0.68–1.44). For the cohort without HRRm, futility was declared based on prespecified criteria. The secondary endpoints of time to symptomatic progression and time to initiation of cytotoxic chemotherapy were improved with the combination therapy in the HRRm and *BRCA* mutation cohorts.

A second interim analysis of MAGNITUDE included a prespecified, inverse probability censoring weighting analysis of OS, which was designed to account for the receipt of subsequent therapies, including PARP inhibitors.¹²⁶ Results of this analysis suggest that there may be an OS benefit for the combination therapy (HR, 0.54; 95% CI, 0.33–0.90; nominal $P=.0181$).

The incidence of grade 3–4 adverse events was higher with the combination of niraparib plus abiraterone compared with placebo and abiraterone (67.0% vs 46.4%).¹²⁵ Anemia (28.3% vs 7.6%) and hypertension (14.6% vs 12.3%) were the most reported grade 3 or higher adverse events. Overall, the combination was tolerable, and QOL was maintained.

Based on these results, the FDA approved niraparib plus abiraterone for the treatment of patients with *BRCA* mutation mCRPC in August 2023. The panel includes niraparib plus abiraterone as a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had

treatment in the setting of mCRPC. This is a category 1 recommendation for those without prior docetaxel or prior novel hormone therapy. It is a category 2A recommendation for those with prior docetaxel and no prior novel hormone therapy. Use of niraparib/abiraterone for those who have received prior novel hormone therapy without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Radiopharmaceuticals for mCRPC

Lutetium Lu 177 Vipivotide Tetraxetan

Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) is a radiopharmaceutical that is administered intravenously and is indicated for prostate-specific membrane antigen (PSMA)-positive M1 CRPC that has been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. The active moiety is a radionuclide that delivers radiation to PSMA-expressing and surrounding cells, inducing DNA damage that leads to cell death. The approval of Lu-177-PSMA-617 was based on the international, open-label phase III VISION trial of 831 patients with M1 CRPC and PSMA-positive metastatic lesions. Patients in VISION were previously treated with at least one androgen receptor-directed therapy and one or two taxane-based chemotherapy regimens.¹²⁷ Patients had at least one PSMA-positive metastatic lesion and no PSMA-negative lesions determined by gallium-68 (Ga-68) labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard of care (abiraterone, enzalutamide, bisphosphonates, radiation therapy, denosumab, and/or glucocorticoids) and Lu-177-PSMA-617 (7.4 GBq or 200 mCi every 6 weeks for 4–6 cycles) or standard of care alone.

The median OS was improved in the Lu-177-PSMA-617 group compared with the control group (15.3 vs 11.3 months; HR, 0.62; 95% CI, 0.52–0.74; $P<.001$). Similarly, the median PFS was improved in the Lu-177-PSMA-617 group compared with the control group (8.7 vs 3.4 months; HR, 0.40; 99.2% CI, 0.29–0.57; $P<.001$). The incidence of grade ≥ 3 adverse events (particularly anemia, thrombocytopenia, lymphopenia, and fatigue) was significantly higher in the Lu-177-PSMA-617 group compared with the control group.¹²⁷

The NCCN Prostate Cancer Panel recommends Lu-177-PSMA-617 as a category 1, useful in certain circumstances, treatment option for patients with ≥ 1 PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy. PSMA-negative lesions are

defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥ 1.0 cm, lymph nodes ≥ 2.5 cm in short axis, and solid organ metastases ≥ 1.0 cm in size. Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177-PSMA-617, the panel believes that F-18 piflufolastat PSMA and F-18 flotufolastat PSMA can also be used in the same space due to multiple reports describing the equivalency of these imaging agents.

Radium-223

In May 2013, the US FDA approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of mCRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase III, randomized trial (ALSYMPCA) that included 921 patients with symptomatic CRPC, two or more bone metastases, and no known visceral disease.¹²⁸ Fifty-seven percent of the patients received prior docetaxel, and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6-monthly radium-223 intravenous injections or placebo. Compared with placebo, radium-223 significantly improved OS (median, 14.9 vs 11.3 months; HR, 0.70; 95% CI, 0.058–0.83; $P < .001$) and prolonged time to first SRE (median, 15.6 vs 9.8 months). Preplanned subset analyses showed that the survival benefit of radium-223 was maintained regardless of prior docetaxel use.¹²⁹ ITT analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.¹³⁰ Grade 3–4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.¹²⁸ Fecal elimination of the agent led to generally mild nonhematologic side effects, which included nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of QOL in ALSYMPCA.¹³¹

The multicenter, international, double-blind, placebo-controlled, phase III ERA 223 trial randomized patients with bone-metastatic chemotherapy-naïve CRPC to abiraterone with or without radium-223.¹³² The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic SKE-free survival in the ITT population was not met. In fact, the addition of radium-223 to abiraterone was associated with an increased frequency of bone fractures compared with placebo. The PEACE III trial (ClinicalTrials.gov identifier: NCT02194842) is also comparing radium-223 in combination with a secondary hormonal therapy to secondary hormone therapy alone in patients with mildly symptomatic mCRPC. In this trial, the use of bone protecting agents (denosumab or zoledronic acid) was made mandatory following results from ERA 223. The cumulative incidence of fractures at 1.5 years in

patients who received a bone-protecting agent was 2.8% in participants receiving radium-223 plus enzalutamide and 3.9% in those receiving enzalutamide alone.¹³³ In the absence of bone agents, these numbers were 45.9% and 22.3%, respectively. This result suggests that radium-223 combined with a secondary hormone therapy may be safe if preventive administration of a bone agent is used. The panel awaits further efficacy data before recommending radium-223 in combination with a secondary hormonal therapy.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.⁵¹ Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.⁵¹ It is not recommended for use in combination with docetaxel or any other systemic therapy except ADT. It should not be used in patients with visceral metastases. Based on the PEACE III results described previously, all patients receiving radium-223 should be given concomitant denosumab or zoledronic acid.

Small Cell/Neuroendocrine Prostate Cancer

De novo small cell carcinoma in untreated prostate cancer occurs rarely and is very aggressive.¹³⁴ Treatment-associated small cell/neuroendocrine prostate cancer that occurs in patients with mCRPC is more common.¹³⁵ In a multi-institution prospective series of 202 consecutive patients with mCRPC, all of whom underwent metastatic biopsies, small cell/neuroendocrine histology was present in 17%.¹³⁵ Patients with small cell/neuroendocrine tumors and prior abiraterone and/or enzalutamide had a shorter OS when compared with those with adenocarcinoma and prior abiraterone and/or enzalutamide (HR, 2.02; 95% CI, 1.07–3.82). Genomic analysis showed that DNA repair mutations and small cell/neuroendocrine histology were almost mutually exclusive.

Small cell/neuroendocrine carcinoma of the prostate should be considered in patients with disease that no longer responds to ADT and who test positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.¹³⁶ Those with initial Grade Group 5 are especially at risk. Biopsy of accessible metastatic lesions to identify patients with small cell/neuroendocrine histomorphologic features is recommended in patients with mCRPC.

These patients may be treated with cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, cabazitaxel/carboplatin).^{82,137,138} Physicians should consult the NCCN Guidelines for Small Cell Lung Cancer for additional options in the first and subsequent lines of therapy (available at NCCN.org), because the behavior of small cell/neuroendocrine

carcinoma of the prostate is similar to that of small cell carcinoma of the lung.

Additional Treatment Options for Bone Metastases

In a multicenter study, 643 patients with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every 3 weeks or placebo.¹³⁹ At 15 months, fewer patients in the zoledronic acid 4-mg group than patients in the placebo group had SREs (33% vs 44%; $P=.02$). An update at 24 months also revealed an increase in the median time to first SRE (488 vs 321 days; $P=.01$).¹⁴⁰ No significant differences were found in OS. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications. Earlier use of zoledronic acid in patients with castration-sensitive prostate cancer and bone metastases is not associated with lower risk for SREs, and in general should not be used for SRE prevention until the development of mCRPC.¹⁴¹

The randomized TRAPEZE trial used a 2×2 factorial design to compare clinical PFS (pain progression, SREs, or death) as the primary outcome in 757 patients with bone mCRPC treated with docetaxel alone or with zoledronic acid, 89Sr, or both.¹⁴² The bone-directed therapies had no statistically significant effect on the primary outcome or on OS in unadjusted analysis. However, adjusted analysis revealed a small effect for 89Sr on clinical PFS (HR, 0.85; 95% CI, 0.73–0.99; $P = 0.03$). For secondary outcomes, zoledronic acid improved the SRE-free interval (HR, 0.78; 95% CI, 0.65–0.95; $P = 0.01$) and decreased the total SREs (424 vs 605) compared with docetaxel alone.

Denosumab was compared with zoledronic acid in a randomized, double-blind, placebo-controlled study in patients with CRPC.¹⁴³ The absolute incidence of SREs was similar in the 2 groups; however, the median time to first SRE was delayed by 3.6 months by denosumab compared with zoledronic acid (20.7 vs 17.1 months; $P=.0002$ for non-inferiority, $P=.008$ for superiority). The rates of important SREs with denosumab were similar to zoledronic acid and included spinal cord compression (3% vs 4%), need for radiation (19% vs 21%), and pathologic fracture (14% vs 15%).

Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs 6%), arthralgias, and osteonecrosis of the jaw (1%–2% incidence). Most, but not all, patients who develop osteonecrosis of the jaw have preexisting dental problems.¹⁴⁴

Therefore, denosumab every 4 weeks (category 1, preferred) or zoledronic acid every 3 to 4 weeks is recommended for patients with CRPC and bone metastases to prevent or delay disease-associated SREs. SREs include pathologic fractures, spinal cord compression, operation, or EBRT to bone. The optimal duration of zoledronic acid

or denosumab in patients with CRPC and bone metastases remains unclear. A multi-institutional, open-label, randomized trial in 1,822 patients with bone-metastatic prostate cancer, breast cancer, or multiple myeloma found that zoledronic acid every 12 weeks was noninferior to zoledronic acid every 4 weeks.¹⁴⁵ In the every-12-weeks and every-4-weeks arms, 28.6% and 29.5% of patients experienced at least 1 SRE within 2 years of randomization, respectively.

Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of osteonecrosis of the jaw.¹⁴⁶ If invasive dental surgery is necessary, therapy should be deferred until the dentist confirms that the patient has healed completely from the dental procedure. Supplemental calcium and vitamin D are recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronic acid.

Monitoring of creatinine clearance is required to guide dosing of zoledronic acid. Zoledronic acid should be dose reduced in patients with impaired renal function (estimated creatinine clearance 30–60 mL/min) and held for creatinine clearance <30 mL/min. Denosumab may be administered to patients with impaired renal function or even patients on hemodialysis; however, the risk for severe hypocalcemia and hypophosphatemia is greater, and the dose, schedule, and safety of denosumab have not yet been defined. A single study of 55 patients with creatinine clearance <30 mL/min or on hemodialysis evaluated the use of 60 mg dose denosumab.⁵¹ Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with repletion as needed.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases. The use of palliative, systemic radiation with either 89Sr or 153Sm with or without focal EBRT remains an option, though they are seldom used these days with other available options (see “Radium-223”, page 1089). EBRT alone is also an option.

Clinical research on the prevention or delay of disease spread to bone continues. A phase III randomized trial of 1,432 patients with nonmetastatic CRPC at high risk of bone involvement showed that denosumab delayed bone metastasis by 4 months compared with placebo.¹⁴⁷ OS was not improved, and the FDA did not approve denosumab for the prevention of bone metastases.

Considerations for Visceral Metastases

The panel defines visceral metastases as those occurring in the liver, lung, adrenal gland, peritoneum, or brain. Soft tissue/lymph node sites are not considered visceral metastases. In general, fewer data are available on treatment of patients with CRPC and visceral metastases than for those without visceral metastases. This is especially

true in patients who have already received docetaxel and a novel hormone therapy, where most systemic therapies are given a category 2B recommendation.

Sequencing of Therapy in CRPC

The number of treatment options for patients with CRPC has expanded rapidly over the past several years. Although the optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection in some cases.

After abiraterone or enzalutamide, data suggest that giving the alternate novel hormone therapy may not be the optimal strategy considering the availability of other treatment options, including chemotherapy. The CARD trial, for instance, showed that treatment with cabazitaxel significantly improved clinical outcomes over enzalutamide or abiraterone in patients with mCRPC who had been previously treated with docetaxel and the alternate hormonal therapy (abiraterone or enzalutamide).⁷⁷ Furthermore, data suggest cross-resistance between abiraterone and enzalutamide.^{148–151} Results of a randomized, open-label, phase II, crossover trial suggest that the sequence of abiraterone followed by enzalutamide is more efficacious than the reverse.¹⁵²

Some data inform the sequencing of therapies in patients with actionable biomarkers. The multicenter, unblinded, randomized phase II TheraP trial compared PSA response after Lu-177-PSMA-617 vs cabazitaxel in 200 patients with PSMA-positive mCRPC who previously received docetaxel.¹⁵³ Prior androgen receptor-directed therapy was permitted. Among the ITT population, the PSA response rate was 66% in the Lu-177-PSMA-617 arm compared with 37% in the cabazitaxel arm (difference, 29%; 95% CI, 16–42; $P < .0001$). These numbers were 66% and 44%, respectively, in those that received treatment (difference, 23%; 95% CI, 9–37; $P = .0016$). Furthermore, grade 3–4 adverse events were less frequent in the Lu-177-PSMA-617 arm than in the cabazitaxel arm (33% vs 53%). Results

from the phase III PSMAfore trial (ClinicalTrials.gov identifier: NCT04689828), which may inform the choice between Lu-177-PSMA-617 and switching to a different androgen receptor-directed therapy in docetaxel-naïve patients, are awaited. Data for patients with HRRm mCRPC are more limited, but comparative effectiveness research suggests that olaparib may result in superior radiographic PFS than cabazitaxel in patients with *BRCA1* or *BRCA2* mutations and prior treatment with docetaxel.¹⁵⁴

No chemotherapy regimen has demonstrated improved survival or QOL after cabazitaxel or cabazitaxel/carboplatin, although several systemic agents other than mitoxantrone have shown palliative and radiographic response benefits in clinical trials (ie, carboplatin, cyclophosphamide, doxorubicin, vinorelbine, carboplatin/etoposide, docetaxel/carboplatin, gemcitabine/oxaliplatin, paclitaxel/carboplatin^{155–164}). No survival benefit for these combination regimens over sequential single-agent regimens has been demonstrated, and toxicity is higher. Treatment with these regimens could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care. Prednisone or dexamethasone at low doses may provide palliative benefits in the chemotherapy-refractory setting.¹⁶⁵ Participation in a clinical trial is encouraged.

Summary

The intention of these guidelines is to provide a framework on which to base treatment decisions. Prostate cancer is a complex disease, with many controversial aspects of management and with a dearth of sound data to support some of the treatment recommendations. Several variables (including adjusted life expectancy, disease characteristics, predicted outcomes, and patient preferences) must be considered by the patient and physician to tailor prostate cancer therapy for the individual patient.

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Individual Disclosures for the NCCN Prostate Cancer Panel				
Panel Member; (Spouse/Domestic Partner/ Dependent)	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialization
Nabil Adra, MD, MSc	Bristol Myers Squibb; Exelixis Inc.; Genentech, Inc.; Merck & Co., Inc.	Astellas Pharma US, Inc.; AVEO Pharmaceuticals, Inc.; Bristol Myers Squibb; Exelixis Inc.; sanofi-aventis U.S.	None	Medical oncology
Yi An, MD	None	None	None	Radiotherapy/Radiation oncology
Daniel Barcas, MD, MPH	Movember Foundation; National Cancer Institute	Astellas Pharma US, Inc.; Lathus; Pacific Edge Diagnostics	None	Urology
Rhonda Bitting, MD	None	None	None	Medical oncology
Alan Bryce, MD	Amgen Inc.; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Clovis Oncology; Genentech, Inc.; Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; Promontory Therapeutics	Astellas Pharma US, Inc.; Bayer HealthCare; Novartis Pharmaceuticals Corporation; Verity Pharmaceuticals	Astellas Pharma US, Inc.; Bayer HealthCare; Novartis Pharmaceuticals Corporation; Verity Pharmaceuticals	Medical oncology
Brian Chapin, MD	Blue Earth Diagnostics; Regeneron Pharmaceuticals, Inc.	Blue Earth Diagnostics; Janssen Pharmaceutical Products, LP; Johnson & Johnson; Merck & Co., Inc.; Pfizer Inc.	None	Urology
Heather H. Cheng, MD, PhD*	Clovis Oncology; Color Health, Inc.; Janssen Pharmaceutical Products, LP; Promontory Therapeutics (formerly Phosplatin)	None	None	Medical oncology
Anthony Victor D'Amico, MD, PhD	None	None	None	Radiotherapy/Radiation oncology
Neil Desai, MD, MHS	Bayer HealthCare; Boston Scientific Corporation; Pfizer Inc.; Telix Pharmaceuticals	Boston Scientific Corporation	Ultimate Medical Academy (CME Lecture)	Radiotherapy/Radiation oncology
Tanya Dorff, MD	None	AstraZeneca Pharmaceuticals LP; Bayer HealthCare; sanofi-aventis U.S.	None	Medical oncology
James A. Eastham, MD	None	None	None	Urology
Thomas A. Farrington	None	None	Bayer HealthCare; Exact Sciences; Janssen Pharmaceutical Products, LP; Pfizer Inc.	Patient advocate
Xin Gao, MD	ALX Oncology; Aravive; Arvinas; Bayer HealthCare; Exelixis Inc.; Loxo Oncology; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Nuvation Bio; Poseida Therapeutics; Regeneron Pharmaceuticals; Takeda Pharmaceuticals North America, Inc.; TopAlliance Biosciences	Flare Therapeutics, Inc.; PathAI, Inc.	None	Medical oncology
Shilpa Gupta, MD	Bristol Myers Squibb; E, MD Serono; Exelixis Inc.; Genentech, Inc.; Gilead Sciences, Inc.; Immunomedics, Inc.; Merck & Co., Inc.; Pfizer Inc.; Seattle Genetics, Inc.	Bayer HealthCare; Bristol Myers Squibb; E, MD Serono; Gilead Sciences, Inc.; Merck & Co., Inc.; Pfizer Inc.; SeaGen	Gilead Sciences, Inc.	Medical oncology
Thomas Guzzo, MD, MPH	None	None	None	Urology
Joseph E. Ippolito, MD, PhD	None	None	None	Diagnostic/Interventional radiology
Michael R. Kuettel, MD, MBA, PhD	None	None	None	Radiotherapy/Radiation oncology
Joshua M. Lang, MD, MS	None	4D Pharma; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Foundation Medicine; Gilead Sciences, Inc.; Immunomedics, Inc.; Janssen Pharmaceutical Products, LP; Pfizer Inc.	None	Medical oncology
Tamara Lotan, MD	AIRA Matrix; DeepBio; Myriad Genetic Laboratories, Inc.; Roche Laboratories, Inc.	None	None	Pathology
Rana R. McKay, MD	Arteria; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol Myers Squibb; Calibr; Eli Lilly and Company; Exelixis Inc.; Genentech, Inc.; Janssen Pharmaceutical Products, LP; Merck & Co., Inc.; Oncternal; Pfizer Inc.; Poseida; Scholar Rock; Sorrento Therapeutics; Tempus	AstraZeneca Pharmaceuticals LP; AVEO Pharmaceuticals, Inc.; Bayer HealthCare; Bristol Myers Squibb; Caris Life Sciences; Eisai Inc.; Eli Lilly and Company; Exelixis Inc.; Janssen Pharmaceutical Products, LP; Merck & Co., Inc.; Myovant; Novartis Pharmaceuticals Corporation; Pfizer Inc.; sanofi-aventis U.S.; SeaGen; Sorrento Therapeutics; Telix; Tempus	None	Medical oncology
Todd Morgan, MD	None	A3P Biomedical; Blue Earth Diagnostics; Tempus	None	Urology
George Netto, MD*	None	None	None	Pathology
Julio M. Pow-Sang, MD	None	AngioDynamics	None	Urology
Robert Reiter, MD, MBA	None	Lanthus; Pfizer Inc.	Bayer HealthCare; Genomic Health, Inc.; Janssen Pharmaceutical Products, LP; MDx Health; Pfizer Inc.	Urology
Mack Roach III, MD*	None	Accuray Incorporated; Pfizer Inc.	Janssen Pharmaceutical Products, LP	Radiotherapy/Radiation oncology
Tyler Robin, MD, PhD	None	None	None	Radiotherapy/Radiation oncology
Stan Rosenfeld	None	None	None	Patient advocate
Edward M. Schaeffer, MD, PhD	None	Astellas Pharma US, Inc.; Lanthus; Pfizer Inc.	None	Urology
Ahmad Shabsigh, MD	None	None	None	Urology
Daniel Spratt, MD	Janssen Pharmaceutical Products, LP	Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Elekta (radiotherapy company); Novartis Pharmaceuticals Corporation; Pfizer Inc.	None	Radiotherapy/Radiation oncology
Sandy Srinivas, MD	AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol Myers Squibb; Eisai Inc.; Exelixis Inc.; Genentech, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Regeneron Pharmaceuticals, Inc.; Seattle Genetics, Inc.	AstraZeneca Pharmaceuticals LP; AVEO Pharmaceuticals, Inc.; Bristol Myers Squibb; Janssen Pharmaceutical Products, LP; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Seattle Genetics, Inc.	None	Medical oncology; Urology
Benjamin A. Teply, MD	Bellicum Pharmaceuticals; Bristol Myers Squibb; QED Therapeutics	Eli Lilly and Company; Exelixis Inc.; Pfizer/Myovant; sanofi-aventis U.S.	None	Medical oncology
Jonathan Tward, MD, PhD	Bayer HealthCare; Myriad Genetic Laboratories, Inc.	Myriad Genetic Laboratories, Inc.	None	Radiotherapy/Radiation oncology
Richard Valicenti, MD	None	None	None	Radiotherapy/Radiation oncology
Jessica Karen Wong, MD	None	None	None	Radiotherapy/Radiation oncology

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*The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:

Heather H. Cheng, MD, PhD: UpToDate

George Netto, MD: Exact Sciences Corp.

Mack Roach III, MD: UpToDate, WolterKluwer.