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 (mCRPC), 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.


ABSTRACT

The 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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Disclosures for the NCCN Prostate Cancer Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

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 NCCN Guidelines for Prostate Cancer are available free of charge at NCCN.org.
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.\(^1\) 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 overdetection (see the NCCN Guidelines for Prostate Cancer Early Detection, available at NCCN.org). This reduced overdetection along with the use of active surveillance in appropriate patients should reduce overtreatment...
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 Castration-Sensitive Prostate Cancer,” 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 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.
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; \( P \leq 0.0001 \)).

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. 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). 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.

The second randomized trial (STAMPEDE) of 1,917 patients with castration-sensitive prostate cancer showed similar OS benefits. However, unlike LATITUDE, STAMPEDE eligibility permitted patients with high-risk N0,M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >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; \( P \leq 0.0001 \)) 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 \( \geq 70 \) years (HR, 0.94 vs HR, 0.51). Patients \( \geq 70 \) 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; \( P \leq 0.0001 \)) 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...
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). 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. 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.

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).

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...
(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. 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 PSA levels and clinical PFS. An additional analysis was triggered at 470 deaths. 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). 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). 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. 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). CHAARTED randomized 790 patients with metastatic, castration-sensitive prostate cancer to docetaxel (75 mg/m² intravenous every 3 weeks × 6 doses) plus ADT or ADT alone. 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).
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 CAHARTED 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. The results in the M1 population confirmed the survival advantage of adding docetaxel (75 mg/m² intravenous every 3 weeks for 6 doses) to ADT seen in the CAHARTED 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 CAHARTED).

Patients with low metastatic burden did not have definitively improved survival outcomes in the ECOG CAHARTED study or a similar European trial (GETUG-AFU 15). 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. 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. 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
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 \(\geq3\) 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 the 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.
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 in a median overall survival that was 14 months longer (8 years) than those in the intermittent arm (6.8 years).

ADT options are:
- M0 RR 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

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

Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider monitoring while additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and 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.
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 intolerability, with consideration of the fact that even in cases in which PSA remains undetectable, bone imaging may reveal progression.63-65 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 M0 or M1 CRPC

- Androgen receptor activation and autoandrogenic 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 antandrogen
    - 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 antandrogen (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 32 months, final overall survival analysis showed an improved median overall survival with apalutamide versus placebo (73.5 months vs. 59.3 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.
A phase III study of patients with M0 CRPC and a PSADT ≥10 months showed that in the ATAR arm (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 (2.3% 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 BID) compared to prednisone alone improved radiographic progression-free survival (rPFS) 3 months 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 III 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 with 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 I recommendations. Both drugs are suitable options for patients who are not good candidates to receive docetaxel.

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%); hyperphosphatemia (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).
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 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 ≥50% 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
abiraterone with prednisone, were switched to abiraterone with 0.5 mg/day dexamethasone. The primary end-point 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. 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 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 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 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

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. The enzalutamide group had significantly better PFS (defined as PSA progression, soft tissue progression, or development of additional bony metastases) compared...
• Docetaxel treatment can be attempted after progression on a novel hormone therapy in patients with metastatic CRPC whose cancer has not developed any 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 for sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens. See NCCN Guidelines for Hematopoietic Growth Factors2 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, BNP1, CDX2, CHEK1, CHEK2, FANC1, PALB2, RAD51B, RAD51C, RAD51D, or RAD52) 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 a 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, CDK13, 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-J).54 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-J). 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 prior metastases, life expectancy ≥6 months, and ECOG performance status 0–1.

• Sipuleucel-T is not recommended for patients with small cellNEPC.

• 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.

†To view the most recent version of these guidelines, visit NCCN.org.
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. 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. 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). TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1,006 patients. 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. The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared with mitoxantrone plus prednisone.

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. 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. 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.

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. 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, 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. 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.

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. 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; \(P=0.008\)) 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 antidiarreal 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 \(RB1\)). 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 prostastic 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. 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). 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. 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. 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. 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. 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 CPRC is estimated at 2%–5%, 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,
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.\textsuperscript{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).\textsuperscript{113} Furthermore, there were few patients in PROfound with mutations in some of the genes. For example, only 4 patients had *BRIPI* 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.\textsuperscript{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), and drug-induced pneumonia. Rare but serious side effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonia, and a theoretical risk of myelodysplasia or acute myeloid leukemia.

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. 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.

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). 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. 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.

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. Additional preclinical data show that androgen receptor inhibitors can downregulate DNA repair genes, creating a situation similar to that of HRRm. 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).
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.\(^1\)\(^2\) 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.\(^1\)\(^2\) 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.\(^1\)\(^2\) 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.\(^1\)\(^2\) 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.\(^1\)\(^2\) 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 nonBRCA HRR alterations.

Prior therapy also affected the radiographic PFS outcomes in this trial.\(^1\)\(^2\) 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 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 HRm and an additional 247 patients without HRm. 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 HRm 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 HRm 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** HRm (HR, 0.99; 95% CI, 0.68–1.44). For the cohort without HRm, 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 HRm 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. 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%). 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. 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.

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 flutufolastat 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.

**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.\(^{129}\) JTT 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-naive 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. 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; \( P = .01 \)). 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.

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. 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. 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%), arthropalgias, and osteonecrosis of the jaw (1%–2% incidence). Most, but not all, patients who develop osteonecrosis of the jaw have preexisting dental problems.

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. 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. 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. 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. 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.146–151 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 HRKm 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/carboplatin155–164). 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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2. Sartor AO, Tangen CM, Hussain MH, et al. Antiandrogen withdrawal in ca-


Clarke NW, Armstrong AJ, Thiery-Vuillenmin A, et al. Final overall survival (OS) in PROpel: abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2023;41:Suppl;Abstract LBA16.


### Individual Disclosures for the NCCN Prostate Cancer Panel

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<tr>
<th>Panel Member</th>
<th>(Spouse/Domestic Partner/Dependent)</th>
<th>Clinical Research Support/Data Safety Monitoring</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness Testimony Board</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
<th>Specialization</th>
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<td>Nabil Adra, MD, MS</td>
<td></td>
<td>Bristol Myers Squibb, Exelixis Inc.; Genentech Inc.; Merck &amp; Co., Inc.</td>
<td>AstraZeneca Pharmaceuticals LP, AVID Pharmaceuticals LP; Bristol Myers Squibb, Exelixis Inc.; sand-averaged U.S.</td>
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<td>Alex Byrne, MD</td>
<td>Angion Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Cfrau Oncology; Genentech Inc.; Janssen Pharmaceuticals Products LP; Novartis Pharmaceuticals Corporation; Promyted Therapeutics</td>
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<td>Brian Chares, MD</td>
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<td>Anthony Vittorio DiNicolos, MD, PhD</td>
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<td>Tanja Doro, MD</td>
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<td>James A. Eastham, MD</td>
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<td>Xin Gao, MD</td>
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<td>Joseph E. Ipoulos, MD, PhD</td>
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<td>Tanweer Lator, MD</td>
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*The following individuals have disclosures relating to employment/governing board, patient, equity, or royalty: Heather H. Cheng, MD, PhD; UpToDate; George Nett, MD; Ghost Sciences Corp; Mack Rouch II, MD; UpToDate; WolkFakelur.

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