Prostate Cancer, Version 3.2026

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Abstract

The NCCN Guidelines for Prostate Cancer provide a framework on which to base decisions for patients with prostate cancer across the disease spectrum. The Guidelines sections included in this article focus on metastatic castration-sensitive prostate cancer (mCSPC), nonmetastatic castration-resistant prostate cancer (CRPC), and metastatic CRPC (mCRPC). For patients with mCSPC, disease characteristics, such as whether metastases arose synchronously or metachronously and the degree of metastatic burden, impact therapy decisions, including how much treatment intensification is appropriate and when prostate-directed and/or metastasis-directed therapy should be considered. In the mCRPC setting, androgen deprivation therapy is continued with the sequential or concurrent addition of certain androgen receptor pathway inhibitors, 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, biomarkers, the extent and location of metastases, symptoms, and potential side effects.

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Overview

An estimated 313,780 new cases of prostate cancer will be diagnosed in the United States in 2025, accounting for 30% 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. These trends largely reflect the changes in prostate-specific antigen (PSA) screening recommendations. The decrease in PSA screening that followed the 2012 United States Preventive Services Task Force recommendations against routine testing was associated with a rise in the diagnosis of regional and metastatic disease.[2–10]

Researchers further estimate that prostate cancer will account for 11% of male cancer deaths in the United States in 2025, with an estimated 35,770 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 0.5% annual decrease from 2012 through 2022.[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 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 67% higher than in White individuals, with prostate cancer accounting for 44% of cancer diagnoses in Black men and a 1 in 6 lifetime risk of a prostate cancer diagnosis.[11] Black individuals are also more likely to be diagnosed with more aggressive disease and are less likely to

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To view disclosures of external relationships for the NCCN Guidelines panel, go to https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

The full NCCN Guidelines for Prostate Cancer are not printed in this issue of *JNCCN*. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

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have had a PSA test within the past year.[11] The mortality rate from prostate cancer in this population is 2 to 4 times higher than all other racial and ethnic groups; prostate cancer accounts for 17% of male cancer deaths in the United States.[1,11] However, the overall prognosis by race appears similar when patients are treated with the same guideline-concordant care.[12]

Use of PSA for early detection of potentially fatal prostate cancer coupled with the use of imaging and the consideration of risk calculators and/or 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 mCSPC

Androgen deprivation therapy (ADT) with treatment intensification is strongly recommended for patients with metastatic castration-sensitive prostate cancer (mCSPC) (Figure 1, Figure 2, Figure 3, and Figure 4). The use of ADT monotherapy in this setting is discouraged unless there are clear contraindications to

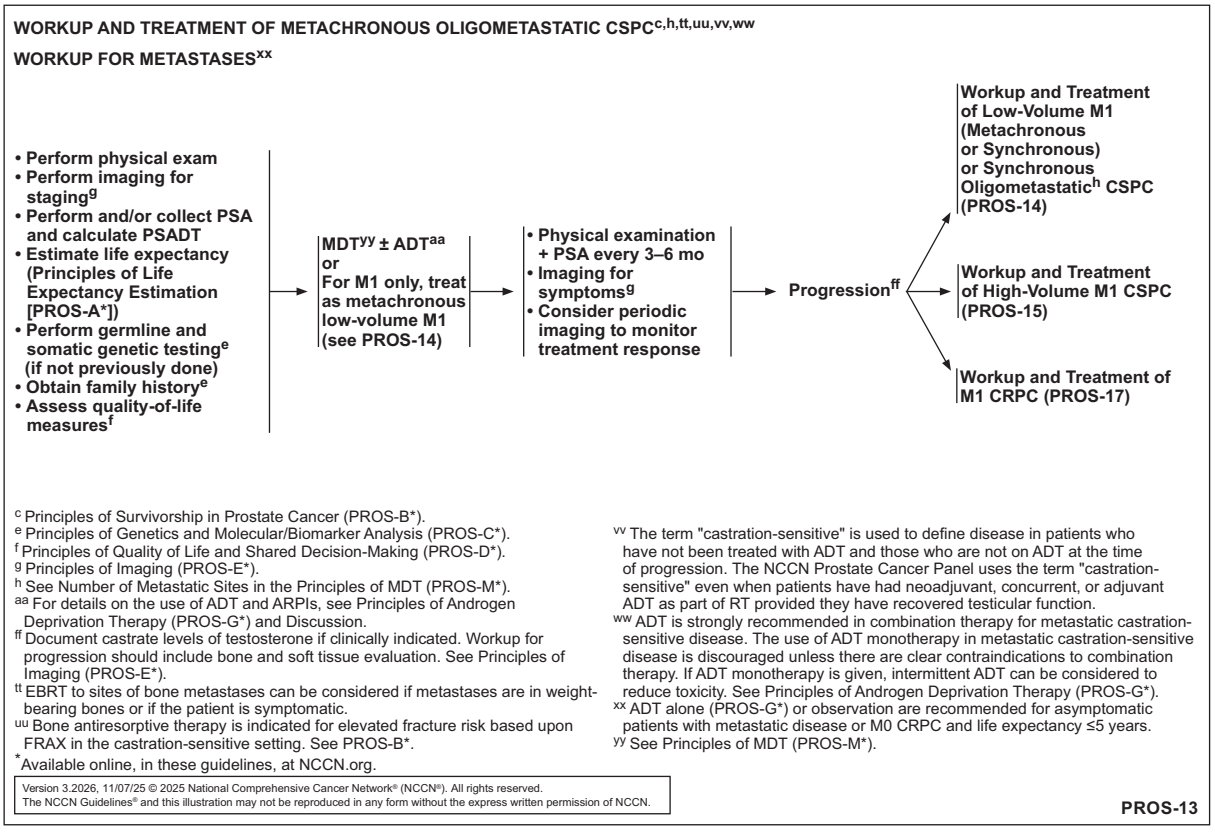

Figure 1. PROS-13. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

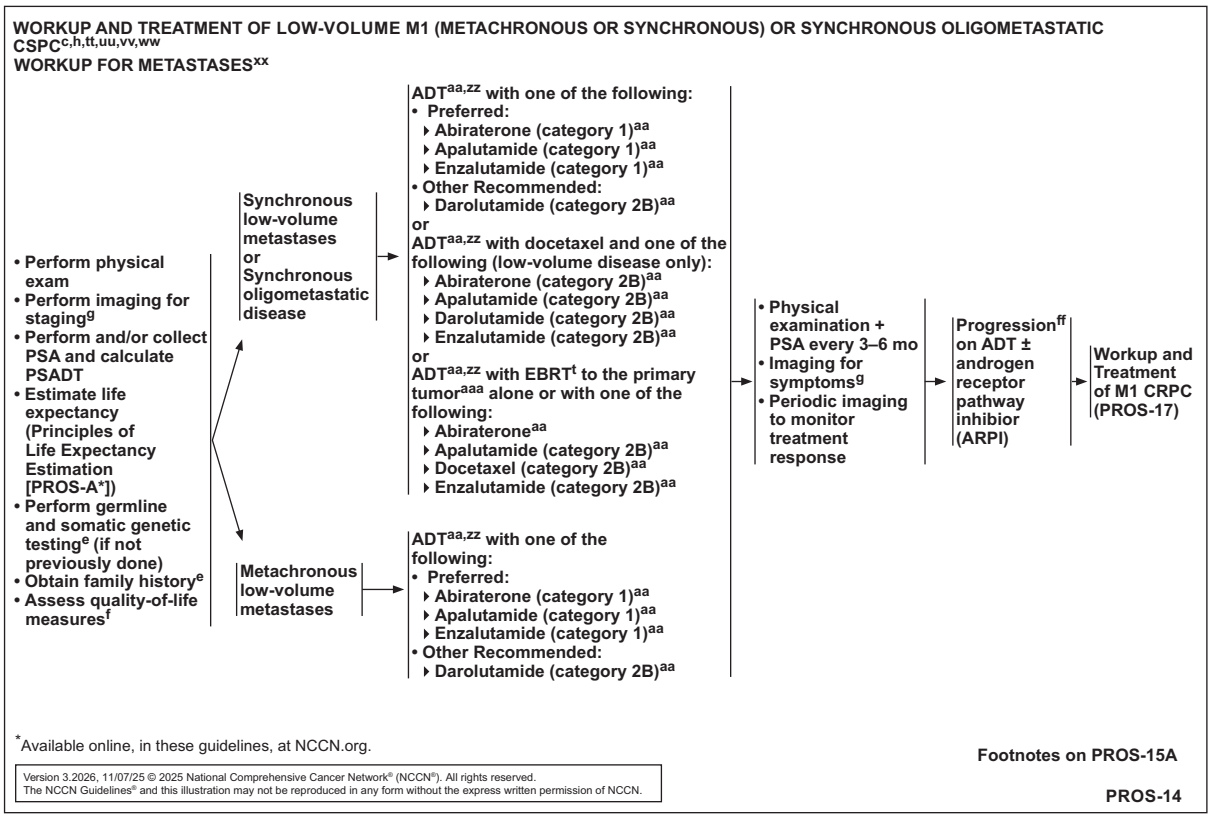

Figure 2. PROS-14. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

combination therapy. Treatment intensification options include doublet therapy of ADT with an androgen receptor pathway inhibitor (ARPI; abiraterone, apalutamide, darolutamide, or enzalutamide); triplet therapy of ADT with docetaxel and one of the same ARPIs; metastasis-directed therapy (MDT) for oligometastases (see "MDT for Oligometastatic CSPC," subsequent section); or ADT with external beam radiation therapy (EBRT) to the primary tumor with or without docetaxel, abiraterone, apalutamide, or enzalutamide for low-metastatic burden (see "EBRT to the Primary Tumor in Low-Metastatic-Burden M1 Disease," available in these guidelines at NCCN.org). The specific recommended therapy options vary depending on whether the metastases were diagnosed in the synchronous or metachronous setting and on whether disease is oligometastatic, low-volume metastatic, or high-volume metastatic.

The data supporting doublet or triplet therapy in this setting are discussed subsequently. For some of the combinations recommended by the panel, supporting data are limited. They are included based on extrapolation from the studies of other agents, since the panel considers the four ARPIs with approval in prostate cancer to be generally interchangeable.

Doublet Therapies for mCSPC

Abiraterone Acetate in mCSPC

In February 2018, the FDA approved abiraterone in combination with prednisone for mCSPC. 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 mCSPC 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-month 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; $P<.0001$).[14]

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

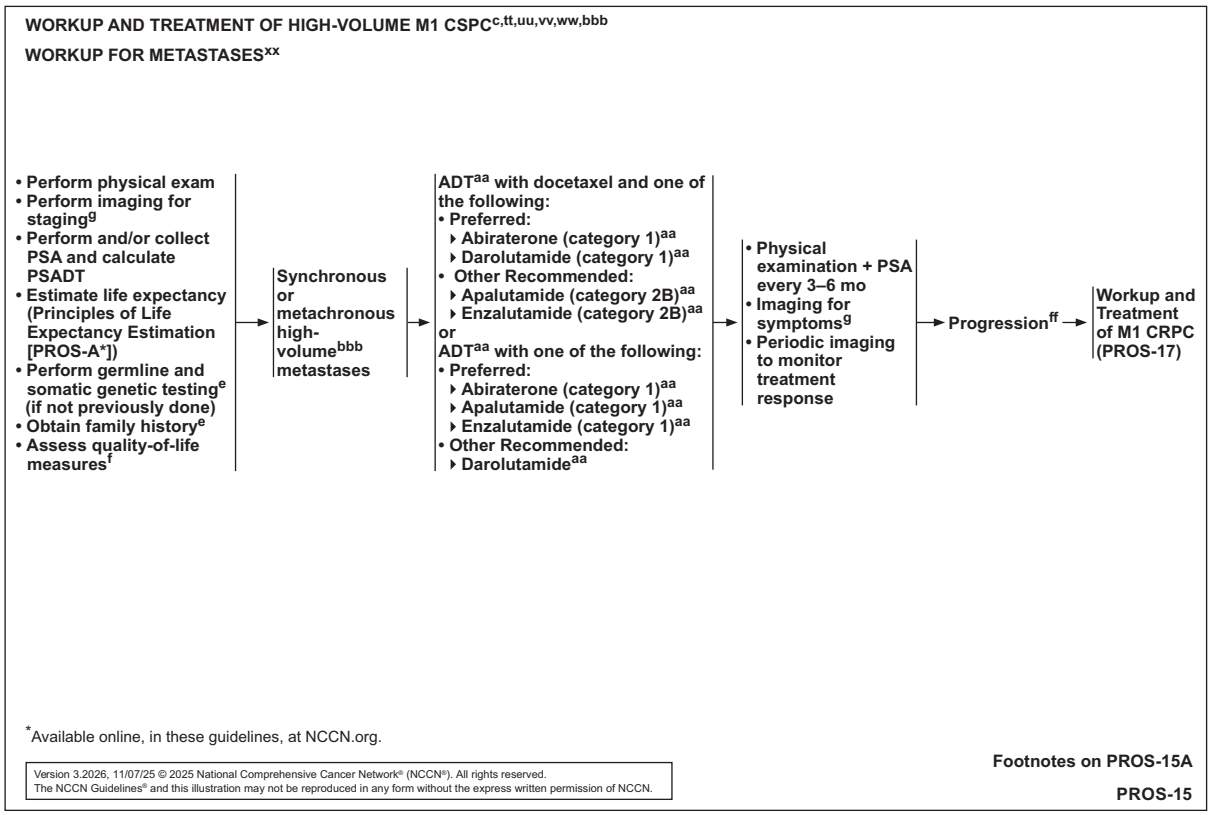

Figure 3. PROS-15. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

enzalutamide at progression, and only 52% of these patients received any life-prolonging therapy.[13]

The second randomized trial (STAMPEDE) of 1,917 patients with CSPC demonstrated similar OS benefits.[16] However, unlike LATITUDE, STAMPEDE eligibility permitted patients with high-risk N0,M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >40, or Gleason score 8–10; n=509), or N1,M0 disease (pelvic nodal metastases; n=369) in addition to patients with metastatic disease, who made up the majority of patients (n=941). Most patients were newly diagnosed, whereas a minority had recurrent, high-risk, or metastatic disease after local therapy (n=98). Thus, STAMPEDE included a heterogeneous mix of patients with high-risk, nonmetastatic, node-positive, or metastatic disease. In patients with M1 disease, treatment with abiraterone plus prednisone was continued until progression. In patients with N1 or M0 disease, 2 years of abiraterone plus prednisolone was used if curative-intent EBRT was used. OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; $P<.0001$) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status. The survival benefit of abiraterone was larger in patients <70 years of age than those ≥70 years (HR, 0.94 vs HR, 0.51). Patients ≥70 years also suffered increased toxicities, which suggests heterogeneity in clinical benefits by age and comorbidity. The secondary endpoint of failure-free survival (FFS), which included PSA recurrence, was improved overall (HR, 0.29; $P<.0001$) and in all subgroups regardless of M1 (HR, 0.31), N1 (HR, 0.29), or M0 (HR, 0.21) status. No heterogeneity for FFS 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 panel to recommend abiraterone with 5-mg once-daily prednisone as a treatment option with ADT for patients with newly diagnosed mCSPC (category 1). Alternatively, the fine-particle formulation of abiraterone can be used with 4 mg methylprednisolone orally twice daily (category 2B; see "Abiraterone Acetate in mCRPC," subsequent section).

The standard formulation of 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 mCRPC," in a subsequent section).[17] The cost savings may reduce financial toxicity and improve adherence in those who will not take or cannot afford the standard dose.

Apalutamide in mCSPC

The double-blind phase 3 TITAN clinical trial randomized 1,052 patients with mCSPC to ADT with apalutamide (240 mg/day) or placebo.[18] Participants were stratified by Gleason score at diagnosis, geographic region, and previous docetaxel treatment. The

FOOTNOTES

[c] Principles of Survivorship in Prostate Cancer (PROS-B*).
[e] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C*).
[f] Principles of Quality of Life and Shared Decision-Making (PROS-D*).
[g] Principles of Imaging (PROS-E*).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M*).
[t] Principles of Radiation Therapy (PROS-J*).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G*) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E*).
[tt] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[uu] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-B*.
[vv] The term "castration-sensitive" is used to define disease in patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[ww] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G*).
[xx] ADT alone (PROS-G*) or observation are recommended for asymptomatic patients with metastatic disease or M0 CRPC and life expectancy ≤5 years.
[zz] Concurrent MDT can be considered in select patients with oligometastatic disease. See Principles of MDT (PROS-M*).
[aaa] EBRT to the primary tumor is associated with an overall survival (OS) benefit in patients with low metastatic burden at the time of diagnosis of metastatic disease, which is defined by bone scan and CT or MRI as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis (Ali A, et al. JAMA Oncol 2021;7:555-563). See Principles of Radiation Therapy (PROS-J).
[bbb] High-volume disease in this setting is defined based on CHAARTED criteria (the presence of visceral metastasis or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis).

*Available online, in these guidelines, at NCCN.org.

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PROS-15A

Figure 4. PROS-15A. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

median follow-up was 22.7 months. Both primary endpoints were met: radiographic progression-free survival (PFS; 68.2% vs 47.5% at 24 months; HR for radiographic progression or death, 0.48; 95% CI, 0.39–0.60; $P<.001$) and OS (82.4% vs 73.5% at 24 months; HR for death, 0.67; 95% CI, 0.51–0.89; $P=.005$). Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease. Health-related QOL was maintained during treatment.[19] At final analysis of TITAN, median OS was improved with apalutamide plus ADT compared with ADT alone after a median follow-up of 44 months (not reached vs 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; $P<.001$).[20]

Apalutamide is a category 1 option for patients with mCSPC. The FDA approved this indication in September 2019.

Enzalutamide in mCSPC

The open-label randomized phase III ENZAMET clinical trial compared enzalutamide (160 mg/day) plus ADT (luteinizing hormone-releasing hormone analogue or surgical castration) with a first-generation antiandrogen (bicalutamide, nilutamide, or flutamide) plus ADT in 1,125 patients with mCSPC.[21] Stratification was by volume of disease, planned use of early docetaxel, planned use of bone antiresorptive therapy, comorbidity score, and trial site. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; $P=.002$). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS. An additional analysis was triggered at 470 deaths.[22] After a median follow-up of 68 months, the 5-year OS rate was again lower in the first-generation antiandrogen group than in the enzalutamide group (HR, 0.70; 95% CI, 0.58–0.84; $P<.0001$). The median OS was not reached.

In the double-blind randomized phase III ARCHES clinical, 1,150 patients with mCSPC were randomized to receive ADT with either enzalutamide (160 mg/day) or placebo. Participants were stratified by disease volume and prior docetaxel use. The primary endpoint was radiographic PFS, which was improved in the enzalutamide group after a median follow-up of 14.4 months (19.0 months vs not reached; HR, 0.39; 95% CI, 0.30–0.50; $P<.001$).[23] At the final, prespecified OS analysis, median OS was not met in either group, but a 34% reduction in the risk of death was observed in those receiving enzalutamide versus placebo (HR, 0.66; 95% CI, 0.53–0.81; $P<.001$).[24] This result could be an underestimate of the effect of enzalutamide, since approximately 32% of the patients assigned placebo crossed over to enzalutamide after unblinding.

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

Enzalutamide is a category 1 option for patients with mCSPC. The FDA approved this indication in December 2019.

Darolutamide in mCSPC

The phase III ARANOTE trial assessed darolutamide with ADT compared with placebo and ADT in 669 patients with mCSPC.[25] The primary endpoint of radiologic PFS was improved in the darolutamide arm compared with the placebo arm (HR, 0.54;

95% CI, 0.41–0.71; $P<.0001$). The benefit was consistent across the low- and high-volume subgroups. Some of the secondary endpoints were also met, including delayed time to mCRPC and time to pain progression. However, a significant improvement in OS was not evident in the current follow-up (HR, 0.81; 95% CI, 0.59–1.12).

The FDA approved this indication for darolutamide in June 2025. The panel include darolutamide with ADT as an option for patients with low- and high-volume mCSPC. Because an OS benefit has not been demonstrated for darolutamide doublet therapy, it is not a category 1 recommendation at this time.

Docetaxel in mCSPC

Docetaxel with ADT has been studied as an upfront option for patients with mCSPC in 2 phase III trials (ECOG 3805/CHAARTED and STAMPEDE).[26,27] CHAARTED randomized 790 patients with mCSPC to docetaxel (75 mg/m^2 intravenously every 3 weeks × 6 doses) plus ADT or ADT alone.[27] 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; $P=.002$).[28] 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 CHAARTED 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 CSPC.[26] The results in the M1 population confirmed the survival advantage of adding docetaxel (75 mg/m^2 intrravenously every 3 weeks × 6 doses) to ADT seen in the CHAARTED 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 CHAARTED).

Patients with low metastatic burden did not have definitively improved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).[27,29,30] Furthermore, the triplet options of ADT with docetaxel and either abiraterone or darolutamide showed improved OS over ADT with docetaxel (see subsequent section). The panel therefore does not include docetaxel with ADT as an option for patients with mCSPC. Rather, patients with high-volume mCSPC who are fit for chemotherapy should be considered for triplet therapy.

Triplet Therapies for mCSPC

Data from the PEACE-1 and ARASENS trials indicate that triplet therapies of ADT with docetaxel and an ARPI—either abiraterone or darolutamide—improve OS over ADT with docetaxel in patients with high-volume metastatic CSPC.[31,32] These trials are discussed subsequntly. Both these combinations are included as category 1, preferred options for patients with high-volume mCSPC, and their use is encouraged for patients with high-volume disease who are fit for chemotherapy. However, the panel notes that no studies have compared doublet therapies (ADT plus an ARPI; discussed previously) to triplet therapies. Therefore, doublet therapies are also suitable options for patients with high-volume metastatic disease.

These triplet combinations are also included as options in the low-volume, synchronous CSPC setting based on results of a meta-analysis, although their use in this setting is controversial and should be reserved for patients who desire aggressive treatment.[33] No data support the use of triplet therapy in low-volume metachronous mCSPC, and they are not recommended in this setting.

Docetaxel Plus Abiraterone in CSPC

PEACE-1 was an international, open-label, randomized, phase III study conducted in 7 European countries.[31] Using a 2 × 2 factorial design, 1,173 patients with de novo metastatic prostate cancer were randomized at a 1:1:1:1 ratio to standard of care (ADT alone or with docetaxel), standard of care with RT, 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 RT, so data were pooled for the analysis of abiraterone efficacy. Consistent with results of older studies, at a median follow-up of 3.5 years, 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; $P=.030$). An OS benefit with abiraterone was also seen in the subset of patients with high metastatic burden as defined by CHAARTED criteria (HR, 0.77; 95% CI, 0.62–0.96), but was not seen in those with low metastatic burden (HR, 0.93; 95% CI, 0.69–1.28).

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 3 therapies compared with those only receiving ADT and docetaxel. The populations receiving the triplet and doublet therapies experienced similar rates of neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥3 adverse events occurred in 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.

Based on these data, the panel includes this regimen as a category 1 option for patients with high-volume mCSPC.

Docetaxel Plus Darolutamide in CSPC

The international, phase III ARASENS trial, the second phase III trial evaluating a triplet therapy, randomized 1,306 patients with mCSPC to receive ADT and docetaxel with either darolutamide or matching placebo.[32] The primary endpoint, 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, 0.57–0.80; $P<.001$). The addition of darolutamide also showed significant benefits over placebo for secondary efficacy endpoints, including time to CRPC (HR, 0.36; 95% CI, 0.30–0.42; $P<.001$), skeletal event–free survival (HR, 0.61; 95% CI, 0.52–0.72; $P<.001$), and time to initiation of subsequent systemic antineoplastic therapy (HR, 0.39; 95% CI, 0.33–0.46; $P<.001$). Subgroup analysis showed a similar improvement in OS in those with high-volume disease as defined by CHAARTED criteria as in the overall population.[34] An OS benefit was not observed in those with low metastatic burden

(HR, 0.68; 95% CI, 0.41–1.13), but median survival was not reached in either arm.

Adverse events of any grade, grade 3 to 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, and the panel includes this regimen as a category 1 option for patients with high-volume mCSPC.

EBRT to the Primary Tumor in Synchronous Low-Volume M1 Disease

Patients with newly diagnosed, low-volume metastatic prostate cancer can be considered for ADT with EBRT to the primary tumor based on results from the randomized controlled phase 3 STAMPEDE trial.[35] In this multicenter, international study, 2,061 patients were randomized to lifelong ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks). The primary outcome of OS by intention-to-treat (ITT) analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; $P=.266$), but EBRT improved the secondary outcome of FFS (HR, 0.76; 95% CI, 0.68–0.84; $P<.0001$). In a preplanned subset analysis, outcomes of patients with high-metastatic burden (defined as visceral metastases; ≥4 bone metastases with ≥1 outside the vertebral bodies or pelvis; or both) and those with low-metastatic burden (all others) were determined. EBRT improved OS (adjusted HR, 0.68; 95% CI, 0.52–0.90), prostate cancer-specific survival (adjusted HR, 0.65; 95% CI, 0.47–0.90), FFS (adjusted HR, 0.59; 95% CI, 0.49–0.72), and PFS (adjusted HR, 0.78; 95% CI, 0.63–0.98) in patients with low-metastatic burden, but not in patients with high metastatic burden. Long-term results have been reported, confirming the benefit of RT to the primary tumor in the setting of ADT with or without docetaxel.[36]

Abiraterone may be added to ADT with EBRT to the primary tumor in patients with low-volume synchronous metastases based on results of the PEACE-1, open-label, randomized trial.[37] In this trial, participants were randomized 1:1:1:1 to ADT alone or with docetaxel (standard of care, SOC), SOC with abiraterone, SOC with radiation to the prostate, or SOC with abiraterone and radiation to the prostate. Results demonstrated that the addition of RT to the primary tumor in patients with low-volume disease treated with abiraterone led to improvements in median radiographic PFS (4.4 vs 7.5 years). RT to the primary tumor also reduced rates of serious genitourinary toxicity regardless of disease volume, and time to castration resistance was delayed in the full population. Thus, some patients with high-volume disease may also benefit from RT to the primary tumor.

In PEACE-1, the benefits of RT to the primary tumor were only seen in patients receiving abiraterone, not in those receiving ADT alone or with docetaxel.[37] However, in a secondary analysis of the STAMPEDE trial, the benefits of RT on OS and FFS in patients with low-volume disease were seen regardless of planned docetaxel use.[38] The panel therefore includes the addition of docetaxel to ADT and EBRT to the primary tumor as a category 2B recommendation for patients with low-volume synchronous mCSPC.

MDT for Oligometastatic CSPC

Treatment of metastatic sites with local therapy with the intent to improve oncologic outcomes (eg, delaying the initiation of systemic therapy or ADT; improving PFS, radiographic PFS, or OS) is known as metastasis-directed therapy, or MDT. MDT has been primarily studied as metastasis-directed RT (MDRT) and with the highly selected use of surgical lymph node dissection. MDRT is delivered at a higher-than-palliative dose to provide durable local control of the areas targeted and is the most used form of MDT.

MDT is used in patients with oligometastatic disease. The number of metastatic sites to define oligometastatic disease remains an evolving space and is impacted by the sensitivity of the imaging modality used. Early studies included patients with 1 to 3 or 1 to 5 metastatic sites by CT, MRI, or bone scan.[39–42] More recent studies allow for up to 10 metastatic sites by prostate-specific membrane antigen (PSMA)-PET imaging (ClinicalTrials.gov identifiers: NCT04787744, NCT06150417, and NCT03721341. The upper limit is not clearly established and is both a function of oncologic limitations and technical limitations of treating numerous metastatic sites. It should be noted that the goal of MDT is generally to treat all metastatic sites, which may include regional lymph nodes and, potentially, the primary tumor if untreated or if there is evidence of local recurrence. The primary tumor in this setting should be counted as a site. The panel notes that general exclusion limits of >5 and >10 metastases by CT, MRI, or bone scan or by PSMA-PET imaging, respectively, are appropriate.

The best evidence supporting the use of MDT in the CSPC setting comes from randomized phase II studies in patients with metachronous oligorecurrent disease.[39,42–44] These trials mostly used MDRT and showed that the approach improved ADT-free survival or PFS over monitoring or ADT. For example, the ORIOLE trial included 54 previously treated patients with 1 to 3 metastases by conventional imaging who were randomized to receive MDRT or observation.[44] Median PFS was better in the MDRT group than in the observation group (not reached vs 5.8 months; HR, 0.30; 95% CI, 0.11–0.81; $P=.002$), and the treatment was well tolerated. STOMP randomized 62 patients with biochemically recurrent CSPC and ≤3 metastases to surveillance or to MDT with surgery or RT.[43] The median ADT-free survival was improved in the MDT arm after a median 3-year follow-up (13 vs 21 months; HR, 0.60; 80% CI, 0.40–0.90; log-rank $P=.11$). In a combined, longer-term analysis of ORIOLE and STOMP, median PFS was longer with MDT compared with observation (pooled HR, 0.44; 95% CI, 0.29–0.66; $P<.001$) after a median follow-up of 52.5 months.[39]

The EXTEND trial included a more heterogeneous group of patients, because 24 of the 87 enrolled patients had no prior definitive therapy to the prostate and 7 patients had mCRPC.[42] Participants had ≤5 metastases amenable to MDRT and were randomized to MDRT with intermittent ADT or to intermittent ADT alone. After a median follow-up of 22 months, median PFS was improved in the MDRT/ADT group compared with the ADT-only group (not reached vs 15.8 months; HR, 0.25; 95% CI, 0.12–0.55; $P<.001$). Analysis of a separate basket of participants in EXTEND who received continuous ADT have also been reported.[45] Results showed that the inclusion of MDT improved

the primary endpoint of PFS in the participants who received continuous ADT (47 vs 22 months; HR, 0.50; one-sided $P=.036$) and in the combined group of intermittent or continuous ADT (36 vs 17 months; HR, 0.45; $P<.001$).

The SABR-COMET phase II study, which enrolled patients with breast, lung, colorectal, and prostate cancers who had a controlled primary tumor and 1 to 5 metastases amenable to MDRT, showed an improvement on OS with an MDT approach.[46] SABR-COMET included 16 patients with prostate cancer; 14 were randomized to the MDRT arm, and 2 were randomized to receive palliative RT. Patients in both arms received palliative systemic therapy as appropriate. After a median follow-up of 51 months, improvements were seen in 5-year OS rate (17.7% vs 42.3%; 95% CI, 0.28–0.56; stratified log-rank $P=.006$) in the total population of 99 patients. A posthoc sensitivity analysis was used to address the imbalance in the distribution of patients with prostate cancer between the 2 arms of the study. When patients with prostate cancer were excluded from the analysis, the 5-year OS rate continued to trend in favor of the MDRT group (16.2% vs 33.1%; stratified log-rank test $P=.085$).

The benefit of adding ADT to MDRT in patients with oligorecurrent CSPC was assessed in the randomized, phase 2 RADIOSA trial.[41] The 105 enrolled patients were randomized to 6 months of ADT with MDRT or MDRT alone. After a median follow-up of 31 months, the median clinical PFS was improved in the group receiving ADT (32.2 vs 15.1 months; HR, 0.43; 95% CI, 0.26–0.72; $P=.001$).

Based on these data, the Panel recommends MDT with or without ADT as an option for patients with metachronous oligometastatic CSPC. These patients may alternatively be treated with ADT plus systemic therapy for low-volume mCSPC with or without concurrent MDT.

There is currently no randomized evidence in the synchronous oligometastatic setting, just single-arm prospective trials and retrospective cohorts. However, the panel believes that concurrent MDT with recommended systemic therapy can be considered in select patients with synchronous oligometastatic disease.

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 defined as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).[47] 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 orchiectomy or a luteinizing hormone-releasing hormone agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL).

Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider monitoring with continued ADT if the PSA doubling time (PSADT) is >10 months (preferred), because these patients will have a relatively indolent disease history (Figure 5).[48] Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (≤10 months) as described below.

For patients who develop mCRPC, metastatic lesion biopsy is recommended, as is microsatellite instability (MSI)/mismatch repair (MMR) testing, if not previously performed. If MSI-high (MSI-H) or MMR deficiency (dMMR) is found, referral to genetic counseling should be made to assess for the possibility of Lynch syndrome (Figure 6). These patients should also have germline and tumor testing to check for mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, *CDK12*) if not done previously.[49] This information may be used for genetic counseling, cascade germline testing for family members, early use of platinum chemotherapy, and understanding eligibility for biomarker-directed treatments or clinical trials. Tumor mutational burden (TMB) testing is also recommended for patients with mCRPC.

ADT is continued in patients with mCRPC while additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, are applied sequentially or concurrently, as discussed in the sections that follow; all patients should receive best supportive care (Figures 7 and 8). The panel defined treatment options for patients with mCRPC based on previous exposure to ARPIs (abiraterone, enzalutamide, darolutamide, or apalutamide) and docetaxel. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior ARPI 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. Evidence to inform the optimal sequence for delivery of these agents in patients with mCRPC is evolving (see "Sequencing of Therapy in CRPC," subsequent section). 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.[50,51] The sequential use of these agents is recommended in patients who remain candidates for further systemic therapy. The panel also notes that pan-cancer, tumor-agnostic treatments can be considered for patients with mCRPC who have actionable mutations. Clinical trial and best supportive care are additional options.

Secondary Hormone Therapy for CRPC

Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of patients receiving ADT.[52,53] Androgen signaling consequent to nongonadal sources of androgen in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel ARPIs demonstrating efficacy in the nonmetastatic CRPC and mCRPC settings dramatically changed the paradigm of CRPC treatment over the past 2 decades.

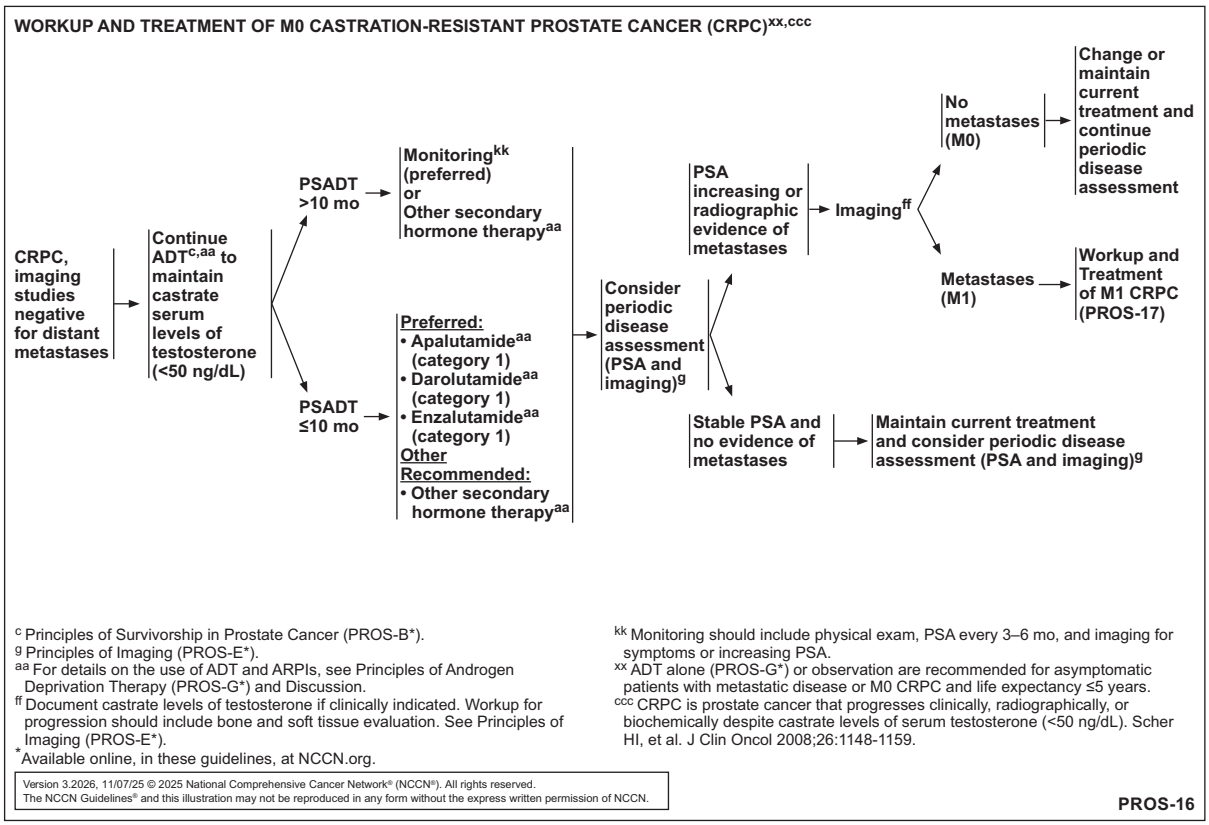


Figure 5. PROS-16. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

Abiraterone Acetate in mCRPC

In April 2011, the FDA approved the androgen synthesis inhibitor, abiraterone, in combination with low-dose prednisone, for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel. This FDA approval in the postdocetaxel, mCRPC setting was based on the results of a phase III, randomized, placebo-controlled trial (COU-AA-301) in patients with mCRPC previously treated with docetaxel-containing regimens.[54,55] Patients were randomized to receive either abiraterone 1,000 mg orally once daily (n=797) or placebo once daily (n=398), and both arms received daily prednisone. In the final analysis, median survival was 15.8 versus 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86; $P<.0001$).[55] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.[55,56]

FDA approval in the predocetaxel setting occurred in December 2012, and was based on the randomized phase III COU-AA-302 trial of abiraterone and prednisone (n=546) versus prednisone alone (n=542) in patients with asymptomatic or minimally symptomatic, mCRPC.[57] Most participants in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary endpoint of radiographic PFS was improved from 8.3 to 16.5 months with abiraterone (HR, 0.53; $P<.001$). OS was improved at final analysis with a median follow-up of 49.2 months (34.7 vs 30.3 months; HR, 0.81; 95% CI, 0.70–0.93; $P=.003$).[58] Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment; PSA declines (62% vs 24% with >50% decline) and radiographic responses (36% vs 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%).

Based on the studies described here, abiraterone is a category 1, preferred option for mCRPC without prior ARPI therapy. It can also be considered in patients with mCRPC following progression on another ARPI, although other therapies are preferred in this setting.

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.[59,60] 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 prior to enrollment was allowed) were randomized to 500 mg daily of the new, fine-particle formulation plus 4 mg methylprednisolone

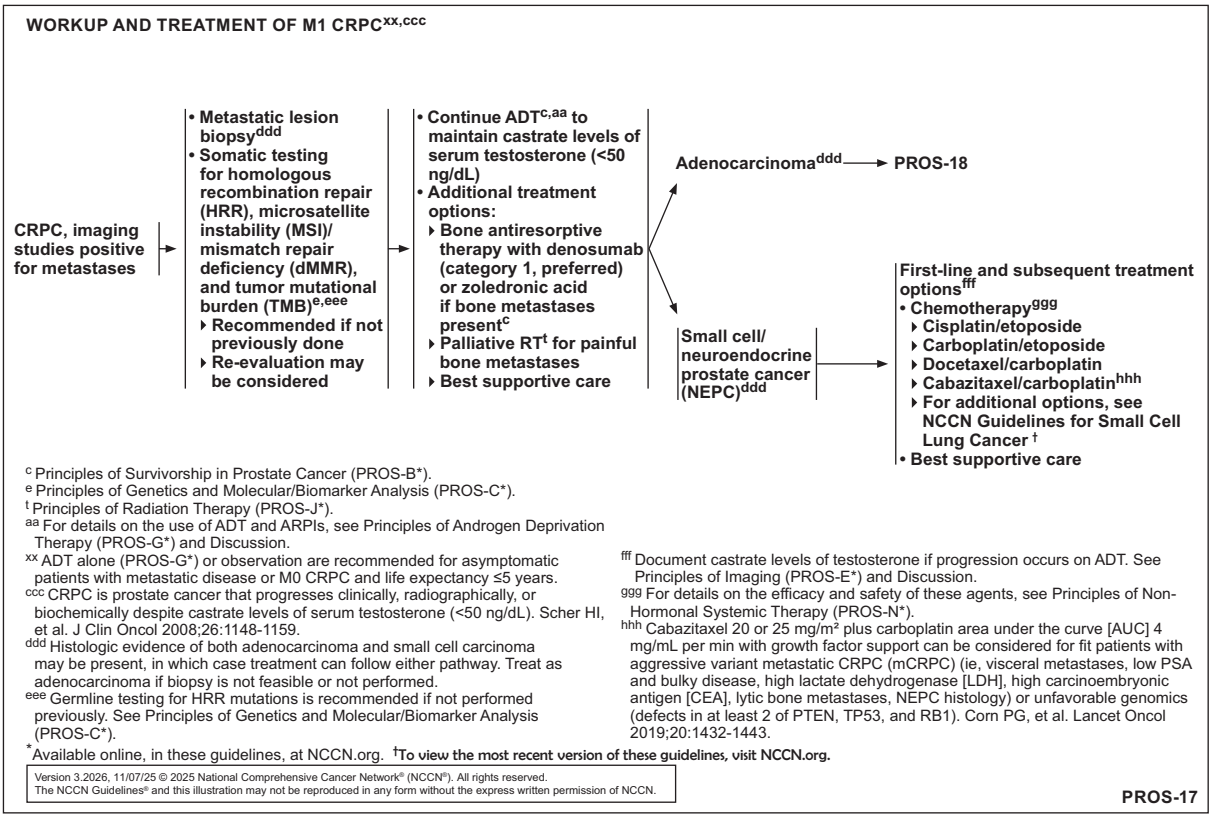


Figure 6. PROS-17. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

orally twice daily or to 1,000 mg of the originator formulation daily plus 5 mg prednisone orally twice daily.[61] 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).

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 mCRPC 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 after 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; therefore, 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 mCRPC

Switching from prednisone to dexamethasone 0.5 mg/day can be considered for patients with mCRPC with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy.[62,63]

The SWITCH study was a single-arm, open-label, phase II study of this approach with 26 enrolled patients.[62] The primary endpoint, the proportion of patients with a PSA decline ≥30% in 6 weeks, was 46.2%. No significant toxicities were observed, and 2 radiologic responses were seen. In another study, 48 consecutive patients with mCRPC, with disease progression on abiraterone with prednisone, were switched to abiraterone with 0.5 mg/day dexamethasone.[63] The primary endpoint of median PFS was 10.35 months, and PSA levels decreased or stabilized in 56% of patients after switching to dexamethasone.

Enzalutamide in M0 and M1 CRPC

In August 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of patients with mCRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase III, placebo-controlled

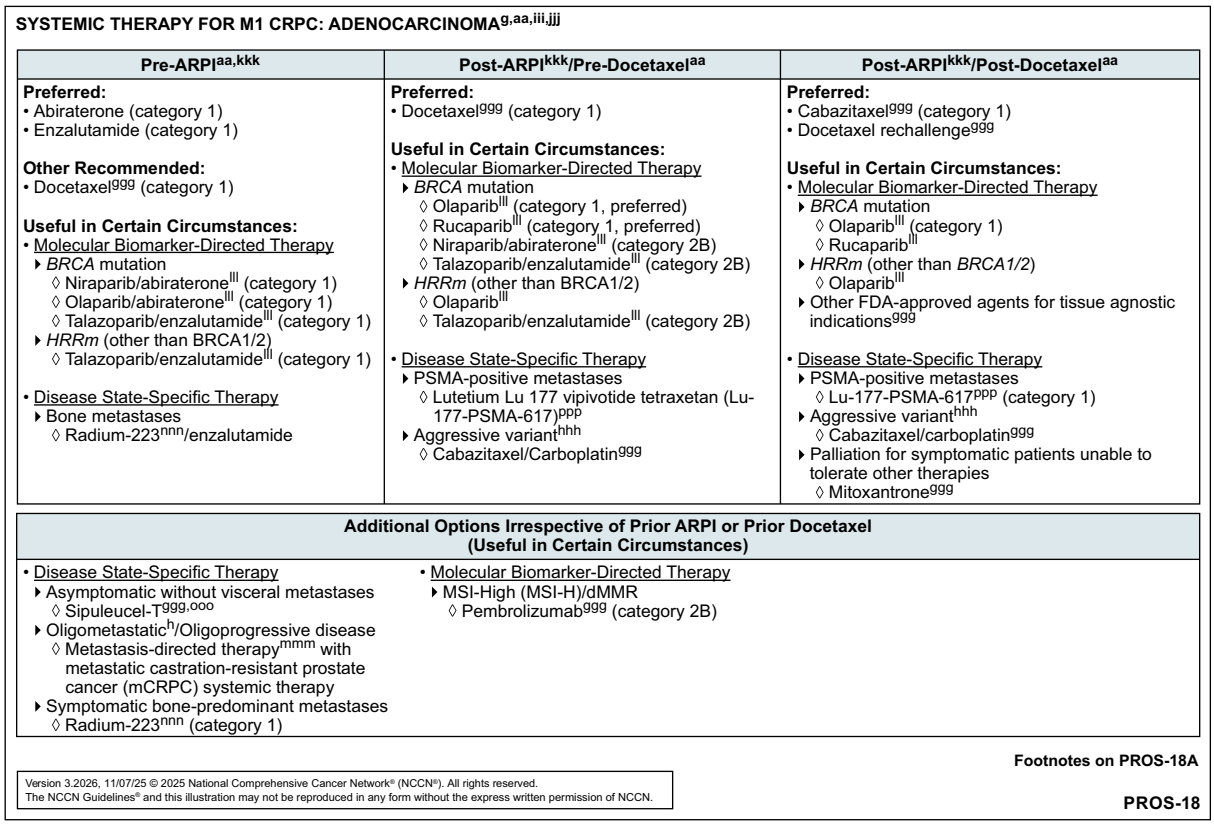


Figure 7. PROS-18. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

AFFIRM trial.[64,65] AFFIRM randomized 1,199 patients to enzalutamide (160 mg daily) 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 were also 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. Patients in the AFFIRM study were maintained on luteinizing hormone-releasing hormone 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.[64,66]

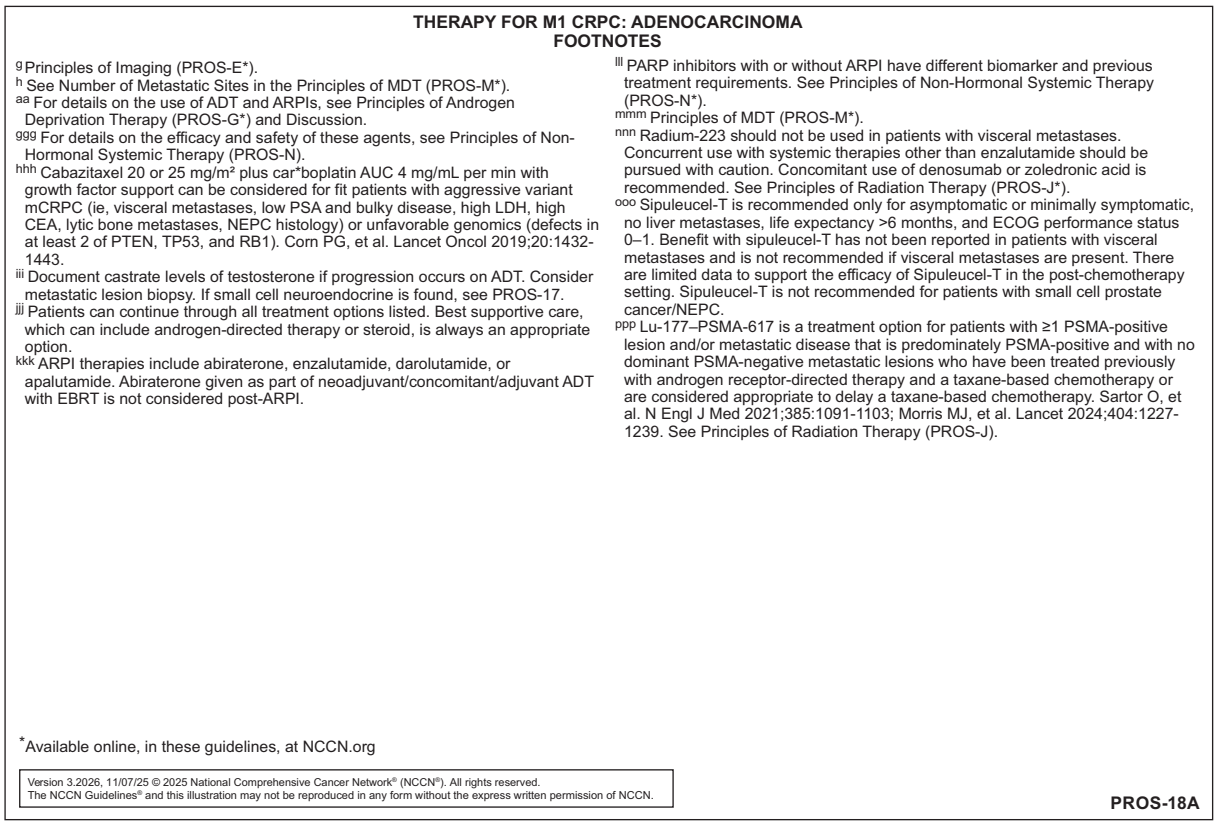
Another phase III trial studied enzalutamide in the pre-chemotherapy setting. The PREVAIL study randomly assigned 1,717 patients with chemotherapy-naïve metastatic prostate cancer to daily enzalutamide or placebo.[67,68] The study was stopped early due to benefits shown in the treatment arm. Compared with the placebo group, the enzalutamide group showed improved median PFS (20.0 vs 5.4 months) and median OS (35.3 vs 31.3 months). Improvements in all secondary endpoints were also observed (eg, the time until chemotherapy initiation or first SRE).

Thus, enzalutamide represents a category 1, preferred treatment option for patients with mCRPC without prior ARPI therapy. It can also be considered in patients with mCRPC with prior exposure to another ARPI, although other therapies are preferred in this setting.

The randomized, double-blind, placebo-controlled phase III PROSPER trial assessed the use of enzalutamide in 1,401 patients with nonmetastatic CRPC.[69] Patients with PSADT ≤10 months were stratified according to PSADT (<6 vs ≥6 months) and use of bone-sparing agents and randomized 2:1 to enzalutamide (160 mg/day) plus ADT or placebo plus ADT. Enzalutamide improved the primary endpoint of metastasis-free survival over placebo (36.6 vs 14.7 months; HR for metastasis or death, 0.29; 95% CI, 0.24–0.35; $P<.0001$). Median OS was longer in the enzalutamide group than in the placebo group (67.0 vs 56.3 months; HR for death, 0.73; 95% CI, 0.61–0.89; $P=.001$).[70] Adverse events included fatigue (33% vs 14%), hypertension (12% vs 5%), major adverse cardiovascular events (5% vs 3%), and mental impairment disorders (5% vs 2%). Patient-reported outcomes from PROSPER indicate that enzalutamide delayed pain progression, symptom worsening, and decrease in functional status, compared with placebo.[71]

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

Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.[64]


THERAPY FOR M1 CRPC: ADENOCARCINOMA
FOOTNOTES

[g] Principles of Imaging (PROS-E*).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M*).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G*) and Discussion.
[ggg] For details on the efficacy and safety of these agents, see Principles of Non-Hormonal Systemic Therapy (PROS-N).
[hhh] Cabazitaxel 20 or 25 mg/m² plus car*boplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant mCRPC (ie, visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, TP53, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.
[iii] Document castrate levels of testosterone if progression occurs on ADT. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-17.
[jjj] Patients can continue through all treatment options listed. Best supportive care, which can include androgen-directed therapy or steroid, is always an appropriate option.
[kkk] ARPI therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered post-ARPI.
[lll] PARP inhibitors with or without ARPI have different biomarker and previous treatment requirements. See Principles of Non-Hormonal Systemic Therapy (PROS-N*).
[mmm] Principles of MDT (PROS-M*).
[nnn] Radium-223 should not be used in patients with visceral metastases. Concurrent use with systemic therapies other than enzalutamide should be pursued with caution. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-J*).
[ooo] Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 months, and ECOG performance status 0–1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. There are limited data to support the efficacy of Sipuleucel-T in the post-chemotherapy setting. Sipuleucel-T is not recommended for patients with small cell prostate cancer/NEPC.
[ppp] Lu-177–PSMA-617 is a 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 or are considered appropriate to delay a taxane-based chemotherapy. Sartor O, et al. N Engl J Med 2021;385:1091-1103; Morris MJ, et al. Lancet 2024;404:1227-1239. See Principles of Radiation Therapy (PROS-J).

*Available online, in these guidelines, at NCCN.org

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PROS-18A

Figure 8. PROS-18A. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 3.2026.

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with nonmetastatic CRPC in February 2018. This approval was based on the phase III SPARTAN trial of 1,207 patients with M0 CRPC and PSADT ≤10 months.[72] Participants were stratified according to PSADT (>6 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.[73]

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; $P=.016$).[74] 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.[75] 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; $P=.003$).[76] 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%).[75]

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.[77–79] However, none of these strategies has been shown to prolong survival in randomized clinical trials. In the mCRPC setting, these options should only be used for select patients who are not candidates for other recommended mCRPC therapies.

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, mCRPC with prior progression on abiraterone.[80] 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; $P=.42$). Crossover 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, and 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

Docetaxel was FDA-approved for mCRPC in May 2004. Two randomized phase III studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive CRPC (TAX 327 and SWOG 9916).[81–83] TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1,006 patients.[82] 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.[83] The SWOG 9916 study showed improved survival with docetaxel when combined with estramustine compared with mitoxantrone plus prednisone.[81]

Thus, docetaxel is a category 1 option for treatment of docetaxel-naïve mCRPC. It is the preferred option post-ARPI in patients without prior docetaxel exposure.

The standard regimen is 75 mg/m^2 every 3 weeks. An alternative to every-3-week docetaxel is a biweekly regimen of 50 mg/m^2. This regimen is based on a large randomized phase 2 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.[84] 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; febrile neutropenia rate was 4% versus 14% and other toxicities and overall QOL were similar.

The duration of docetaxel therapy should be based on the assessment of benefit and toxicities. Treatment with ≥8 cycles of docetaxel may be associated with better OS than fewer cycles in the mCRPC setting.[85]

Retrospective analysis from the GETUG-AFU 15 trial suggests that docetaxel may benefit some patients with CRPC who received docetaxel in the CSPC setting.[86] Thus, the panel believes that docetaxel can be given as a rechallenge after progression on an ARPI in the mCRPC setting if the patient's cancer did not demonstrate definitive evidence of progression on prior docetaxel therapy in either the castration-sensitive setting or the mCRPC setting.

Adverse events associated with docetaxel include neutropenia, leukopenia, febrile neutropenia, neutropenic infections, fluid retention, hypersensitivity reaction, hepatic function impairment, neuropathy, and other low-grade adverse events (eg, fatigue, nausea, vomiting, alopecia, diarrhea).

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/m^2 or mitoxantrone 12 mg/m^2, each with daily prednisone.[87] 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 patients treated with cabazitaxel versus 1.3% of patients treated with mitoxantrone. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in patients treated with cabazitaxel, 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.[88] 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.[89]

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.[90] Cabazitaxel at 25 mg/m^2 with concurrent steroid improved the primary endpoint of radiographic PFS (8.0 vs 3.7 months; HR, 0.54; $P<.0001$) and reduced the risk of death (13.6 vs 11.0 months; HR, 0.64; $P=.008$) compared with abiraterone or enzalutamide in these patients. Cabazitaxel was also associated with an increased rate of pain response and delayed time to pain progression and SREs.[91]

The phase III open-label, multinational, noninferiority PROSELICA study compared 20 mg/m^2 cabazitaxel with 25 mg/m^2 cabazitaxel in 1,200 patients with mCRPC who progressed on docetaxel.[92] 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 suggest that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.[93] Median OS, the primary endpoint, was similar between 20 mg/m^2 cabazitaxel, 25 mg/m^2 cabazitaxel, and 75 mg/m^2 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/m^2

(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 category 1, preferred option after exposure to docetaxel and an ARPI in patients with mCRPC. Cabazitaxel at 20 mg/m^2 every 3 weeks, with or without growth factor support, is the recommended dose for fit patients. Cabazitaxel at 25 mg/m^2 may be considered for healthy patients who opt for more aggressive treatment. Biweekly cabazitaxel at 16 mg/m^2 with prophylactic granulocyte colony-stimulating factor is an option for patients ≥65 years based on results from the phase III CABASTY trial.[94] Using the lower dose significantly reduced the risk of neutropenia/neutropenic complications compared with the 25 mg/m^2 dose with granulocyte colony-stimulating factor. Clinical outcomes were comparable between the 2 groups.

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 population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis) and symptom-directed antidiarrheal agents. Cabazitaxel was tested in patients with hepatic dysfunction in a small, phase I, dose-escalation study.[95] 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 on clinical disease progression or intolerance.

Cabazitaxel/Carboplatin

Cabazitaxel 20 mg/m^2 plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered post-ARPI for fit patients with aggressive variant mCRPC (visceral metastases, low PSA and bulky disease, high lactate dehydrogenase, high carcinoembryonic antigen, lytic bone metastases, and 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.[96] 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 ITT 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, on the other hand, had similar median PFS regardless of treatment (6.5 vs 6.3 months; P=.38).

Sipuleucel-T

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. This autologous cancer "vaccine" involves collection of the white blood cell fraction-containing, antigen-presenting cells from each patient; exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein); and subsequent reinfusion of the cells. The pivotal study was a phase III, multicenter, randomized, double-blind trial (D9902B).[97] Five hundred twelve patients with minimally symptomatic or asymptomatic mCRPC were randomized 2:1 to receive sipuleucel-T or placebo. Of the 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 up for a median of 46.6 months.[98] 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 included in these NCCN Guidelines as an option for asymptomatic patients with mCRPC regardless of prior ARPI or docetaxel, although the panel notes that the data supporting its use postdocetaxel is limited. 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 prostate cancer/ 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. 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.

Pembrolizumab

The FDA approved the tumor-agnostic use of pembrolizumab, an anti-PD-1 antibody, for treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors who have experienced progression 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).[66] All patients received ≥1 prior regimen. Among the noncolorectal cohorts, 2 patients had mCRPC: one experienced a partial objective response, and the other experienced stable disease for >9 months.

Outcomes of additional patients with mCRPC treated with pembrolizumab have been reported.[99–104] 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.[99] Some of the patients also had experienced disease progression on additional therapies (docetaxel for CSPC, abiraterone, and/or sipuleucel-T). Three of the 10 patients showed a near complete PSA response. Two of these three 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 displayed 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 previous therapies for metastatic disease.[101] 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 ARPI that assessed pembrolizumab in patients regardless of MSI status.[105] Cohorts 1 and 2 included patients with programmed cell death ligand 1 (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 to ≥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 includes pembrolizumab as an option for patients with MSI-H or dMMR mCRPC (category 2B). The prevalence of dMMR in metastatic CPRC is estimated at 2%–5%,[100,106,107] 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 tumor-agnostic use in patients with unresectable or metastatic TMB-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Results from prospective biomarker analysis of the multicohort, nonrandomized, open-label, phase 2 KEYNOTE-158 trial support this approval, but this trial did not include any patients with prostate cancer.[108] One retrospective study found that 1.5% of patients with prostate cancer had TMB-H tumors.[107] Of those patients, 8 had received an immune checkpoint inhibitor; 4 patients (50%) experienced a reduction in PSA of ≥50% that lasted at least 1 week. The panel therefore notes that pembrolizumab may be associated with some benefit in patients with mCRPC and TMB ≥10 mut/Mb.

Mitoxantrone

Two randomized trials assessed the role of mitoxantrone in patients with mCRPC.[109,110] Although there was no improvement in OS, palliative responses and improvements in QOL were seen with mitoxantrone.

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

Treatment Options for Patients With DNA Repair Gene Mutations

Early studies suggest germline and somatic mutations in HRR genes (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.[111–113] PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.[114] PARP inhibitor therapy options are discussed subsequently.

DNA repair defects have also been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.[115–119] Platinum agents have shown some activity in patients with CRPC without molecular selection.[120] Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

Results of one study suggested that patients with mCRPC and germline mutations in DNA repair genes may have better outcomes if treated with abiraterone or enzalutamide than with taxanes.[121] However, it should be noted that the response in patients with mCRPC and HRR gene mutations to standard therapies is similar to the response in patients without mutations.[122,123]

Patients with *CDK12* mutations tend to have aggressive disease, with high rates of metastases and short OS. Their disease also does not respond well to hormonal therapy, PARP inhibitors, or taxanes. Two large, multi-institutional, retrospective studies have shown that 11%–33% of patients with mCRPC and *CDK12* mutations experienced disease response to PD-1 inhibitors (ie, nivolumab, pembrolizumab), some with durable responses.[124,125] There are also limited data from phase II trials indicating that ipilimumab plus nivolumab may have some activity against *CDK12*-mutated mCRPC.[126,127] The panel awaits more data on the use of PD-1 inhibition in patients with *CDK12* mutations.

Olaparib

Preliminary clinical data using olaparib suggested favorable activity of this agent in patients with HRR gene mutations, but not in those without HRR mutations.[112,113,128] The phase III PROfound study was a randomized trial evaluating olaparib 300 mg twice daily versus physician's choice of abiraterone or enzalutamide in patients with mCRPC and progression on at least one novel hormonal agent (abiraterone or enzalutamide) and up to one prior taxane agent (permitted but not required).[129] Patients were required to have a somatic or germline HRR gene mutation, and were allocated to one of two cohorts: cohort A comprised patients with *BRCA1/2* or *ATM* mutations, and cohort B comprised patients with a mutation in at least one of 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, or *RAD54L*). The primary endpoint of improving radiographic PFS with olaparib versus abiraterone/enzalutamide was met in cohort A (HR, 0.34; 95% CI, 0.25–0.47; $P<.001$), and radiographic PFS was also superior in the entire study population encompassing cohorts A+B (HR, 0.49; 95% CI, 0.38–0.63; $P<.001$).

In addition, final analysis of PROfound showed that OS was improved with olaparib versus abiraterone/enzalutamide in cohort A (HR, 0.69; 95% CI, 0.50–0.97; $P=.02$), despite the fact that

86 of 131 patients (66%) crossed over to olaparib after disease progression in the control arm.[130]

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.[130] 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).[130] Furthermore, there were few patients in PROfound with mutations in some of the genes. For example, only 4 patients had *BRIP1* mutations (2 in olaparib arm and 2 in control arm), 2 patients had *RAD51D* mutations (both in olaparib arm), and no patients had *RAD51C* mutations.[129] 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 HRR gene mutations 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.

Adverse events that may occur with olaparib treatment include anemia (including that requiring transfusion), fatigue, nausea or vomiting, anorexia, weight loss, diarrhea, thrombocytopenia, creatinine elevation, cough, and dyspnea. Rare but serious side effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonitis, and a theoretical risk of myelodysplasia or acute myeloid leukemia.[129]

Since some patients in PROfound had prior taxane therapy, olaparib use might be reasonable in patients with mCRPC before or after docetaxel treatment. The panel therefore recommends olaparib as an option for patients with mCRPC, previous ARPI, and an HRRm regardless of prior docetaxel therapy. 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*. Olaparib is included in the NCCN Guidelines as a category 1 recommendation for BRCAm mCRPC and is a preferred option for these patients if they have not yet received docetaxel.

Any commercially available analytically and clinically validated somatic tumor and germline assays can be used to identify patients for treatment. The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation; a plasma circulating tumor DNA (ctDNA) assay can be used if a metastatic biopsy is unsafe or not feasible.

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 an ARPI plus one taxane chemotherapy, were treated with rucaparib 600 mg twice daily.[131] The primary endpoint of TRITON2 was the objective response rate in patients with measurable disease, and was 43.5% (95% CI, 31.0%–56.7%) in this *BRCA1/2*-mutated population. 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.[132]

In the randomized phase 3 TRITON3 study, patients with mCRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who have previously received an ARPI but no chemotherapy for mCRPC were randomized 2:1 to rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel).[133] 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*m (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 months; 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, a *BRCA1* or *BRCA2* mutation, and prior treatment with an ARPI. It is a category 1, preferred option predocetaxel. Rucaparib should not be used in patients with HRR gene mutations other than *BRCA1/2*.[134] 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.[131,134]

The preferred method of selecting patients for rucaparib treatment is somatic and germline analysis of *BRCA1* and *BRCA2* from a metastatic biopsy. A ctDNA sample can be used if biopsy is unsafe or not feasible.

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.[135] Additional preclinical data show that androgen receptor inhibitors can downregulate DNA repair genes, creating a situation similar to that of HRR mutation.[136,137] 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 HRR mutations. 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 (ITT population: HR, 0.65; 95% CI, 0.44–0.97; $P=.034$).[113]

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.[138] Prior docetaxel in the localized or mCSPC setting was allowed, but patients were untreated for CRPC. The primary endpoint, 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; $P<.001$). HRR mutations were identified in tumors of 226 patients; 552 patients did not have HRR tumor mutations. The HR for the primary endpoint in those with HRR mutations 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.

Final OS data from PROpel showed that OS was not significantly improved with the abiraterone/olaparib combination therapy in the full cohort after a median follow up of approximately 36.5 months (42.1 vs 34.7 months; HR, 0.81; 95% CI, 0.67–1.00; $P=.054$).[139] In a posthoc exploratory analysis, the BRCAm population saw an OS benefit, with a median OS of 23.0 months in the abiraterone arm and not reached in the combination arm (HR, 0.29; 95% CI, 0.14–0.56). A smaller OS benefit was seen in the HRRm group overall, and no OS benefit was evident in the non-HRRm and the non-BRCAm/other HRRm subgroups.

In May 2023, the FDA approved the combination of olaparib with abiraterone for the treatment of adult patients with BRCAm mCRPC. Based on the results of PROpel, olaparib/abiraterone is included in the NCCN Guidelines as an option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received an ARPI (category 1).

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 HRR mutation and progressive, mCRPC, all of whom received at least one dose of talazoparib.[140] 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"), 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 HRR mutations. The randomized, double-blind, phase III TALAPRO-2 study compared enzalutamide plus talazoparib with enzalutamide plus placebo in 805 patients with untreated mCRPC.[141] HRR gene alteration status and treatment with docetaxel and/or abiraterone in the castration-sensitive setting were used to stratify the randomization. The primary endpoint 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 was 21.9 months (95% CI, 16.6–25.1) for the control group (HR, 0.63; 95% CI, 0.51–0.78; $P<.0001$).

HRR mutations were present in 21% of TALAPRO-2 participants, with *BRCA* alterations being the most common.[141] 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 HRR mutations, talazoparib conferred a 77% lower risk of radiographic progression or death in those with tumor mutations in *BRCA1* or *BRCA2* (HR, 0.23; 95% CI, 0.10–0.53; $P=.0002$), whereas the corresponding reduction was 34% (HR, 0.66; 95% CI, 0.39–1.12; $P=.12$) in those with non-*BRCA* HRR alterations.

Prior therapy also affected the radiographic PFS outcomes in this trial.[141] 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; $P=.12$).

Final results from an HRRm-only cohort of TALAPRO-2 at a median follow-up of 44.2 months showed that median OS was improved with the combination compared with enzalutamide alone (45.1 vs 31.1 months; HR, 0.62; 95% CI, 0.48–0.81; 2-sided $P=.0005$).[142] Median radiographic PFS was also improved with the talazoparib/enzalutamide group compared with the enzalutamide group (30.7 vs 12.3 months; HR, 0.47; 95% CI, 0.36–0.61; $P<.0001$).

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 the results from the first TALAPRO-2 cohort, the FDA approved talazoparib plus enzalutamide for HRRm mCRPC in June 2023. The panel includes talazoparib plus enzalutamide as a category 1 treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in one of certain HRR and other DNA repair genes (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, or *RAD51C*) who have not yet had treatment with an ARPI. Use of talazoparib/enzalutamide for those who have received prior ARPI 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 HRR mutations and an additional 247 patients without HRR mutations.[143] Prior chemotherapy and novel hormonal therapy were allowed in the mCSPC or M0 CRPC settings, and were received by 3.1% and 20.1% of the total HRRm cohort, respectively.

The primary endpoint of MAGNITUDE was radiographic PFS. After a median follow-up of 18.6 months, radiographic PFS was improved for those receiving niraparib in the HRRm group

overall (16.5 vs 13.7 months; HR, 0.73; 95% CI, 0.56–0.96; $P=.022$) as well as in the BRCAm subgroup (16.6 vs 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* HRR mutations (HR, 0.99; 95% CI, 0.68–1.44). For the cohort without HRR mutations, futility was declared based on prespecified criteria. The secondary endpoints of time to symptomatic progression and time to initiation of cytotoxic chemotherapy were improved with the combination therapy in the HRRm and BRCAm 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.[144] 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%).[143] Anemia (28.3% vs 7.6%) and hypertension (14.6% vs 12.3%) were the most reported grade ≥3 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 BRCAm 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 ARPI. Use of niraparib/abiraterone for those who have received a prior ARPI 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.

Radiopharmaceuticals for mCRPC

Lutetium Lu 177 Vipivotide Tetraxetan

Lu-177-PSMA-617 is a radiopharmaceutical that is administered intravenously and is indicated for PSMA-positive mCRPC 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, which induces DNA damage and 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 mCRPC and PSMA-positive metastatic lesions. Patients in VISION were previously treated with at least 1 androgen receptor-directed therapy and 1 or 2 taxane-based chemotherapy regimens.[145] Patients had at least 1 PSMA-positive metastatic lesion and no PSMA-negative lesions determined by Ga-68 labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard of care (abiraterone, enzalutamide, bisphosphonates, RT, 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.[145]

The FDA approved Lu-177-PSMA-617 in the post-ARPI setting in March 2022.

Another randomized controlled phase III trial, PSMAfore, assessed the efficacy of Lu-177-PSMA-617 predocetaxel in 468 patients with mCRPC who experienced disease progression on an ARPI.[146] The primary endpoint of rPFS in the ITT population was improved with Lu-177-PSMA-617 compared with a change in ARPI. At a median of 24.1 months after randomization, median radiographic PFS was 11.6 months in the Lu-177-PSMA-617 group versus 5.6 months in the control group (HR 0.49; 95% CI, 0.39–0.61). There was no difference in OS, but OS data are difficult to interpret because patients were allowed to crossover from an ARPI change to Lu-177-PSMA-617 on radiographic progression, and 57% of patients in the control arm did so. Importantly, there were fewer grade 3–5 toxicities in Lu-177-PSMA-617 arm.

Based on the results of the PSMAfore trial, the FDA expanded the indication for Lu-177-PSMA-617 to include adult patients with PSMA-positive mCRPC who have progressed after ARPI therapy and are considered appropriate candidates for delaying taxane-based chemotherapy.

The NCCN panel recommends Lu-177-PSMA-617 as a treatment option for patients with one or more 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 an ARPI and a taxane-based chemotherapy (category 1) or who have prior ARPI therapy and are considered appropriate to delay 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. The panel notes that Ga-68 PSMA-11, F-18 piflufolastat PSMA, or F-18 flotufolastat PSMA can be used to identify patients eligible for treatment with Lu-177–PSMA-617.

Radium-223

In May 2013, the 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.[147] 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.[148] ITT analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.[149] Grade 3–4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.[147] 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.[150]

The multicenter, international, double-blind, placebo-controlled, phase 3 ERA 223 trial randomized patients with bone-metastatic chemotherapy-naïve CRPC to abiraterone with or without radium-223.[151] The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic skeletal event-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 randomized PEACE-3 trial also compared radium-223 with or without an ARPI in patients who were ARPI-naive.[152] Radium-223 with enzalutamide was compared with enzalutamide therapy alone in 446 patients with mildly symptomatic mCRPC. The use of bone-protecting agents (denosumab or zoledronic acid) was made mandatory after results from ERA 223. The primary endpoint of radiologic PFS was improved in the combination arm compared with enzalutamide alone (16.4 vs 19.4 months; HR, 0.69; 95% CI, 0.54–0.87; $P=.0009$). At a preplanned interim OS analysis, median OS was also improved with the addition of radium-223 (35.0 vs 42.3 months; HR, 0.69; 95% CI 0.52–0.90; $P=.0031$). Grade ≥3 adverse events occurred more commonly in the combination arm (65.6% vs 55.8%) and included hypertension (in 34% of the combination arm), fatigue (6%), fracture (5%), anemia (5%), and neutropenia (5%). Fractures were also more common in the combination arm (24.3% vs 13.4%).

In an earlier safety analysis of PEACE-3, 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.[153] In the absence of bone agents, these numbers were 45.9% and 22.3%, respectively. This result suggests that radium-223 combined with an ARPI may be safe if preventive administration of a bone agent is used.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases in patients with mCRPC regardless of prior therapy. Radium-223 plus enzalutamide is included as an option for patients with bone-metastatic CRPC without prior exposure to an ARPI. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.[66] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[66] Its use in combination with docetaxel or any other systemic therapy except ADT or enzalutamide should be pursued with caution. It should not be used in patients with visceral metastases. All patients receiving radium-223 should be given concomitant denosumab or zoledronic acid.

MDT for mCRPC

Although most data supporting the use of MDT for oligometastatic prostate cancer is in the oligorecurrent CSPC setting, as discussed in detail previously (see "MDT for Oligometastatic CSPC"), MDT has also been studied in the oligoprogressive CRPC. As noted previously, the EXTEND trial included 7 patients with oligoprogressive CRPC, although results of MDT in this subset specifically were not reported.[42]

ARTO is a phase II study that included 157 patients with CRPC and 1 to 3 metastatic lesions who were randomized to receive abiraterone alone or abiraterone with MDRT.[40] The rate of biochemical response (defined as a ≥50% decrease in PSA levels at 6 months compared with baseline), which was the primary endpoint, was 92% in the MDRT group compared with 68.3% in the control group (OR, 4.22; 95% CI, 2.12–8.38; $P<.001$). PFS, a secondary endpoint was also improved with the use of MDRT (HR, 0.35; 95% CI, 0.21–0.57; $P<.001$). A subgroup analysis of ARTO further suggested that MDRT for oligoprogressive mCRPC may result in similar PFS as second-line systemic therapy.[154]

Initial results from the phase II GROUQ-PCS-9 were presented at the 2025 ASCO Genitourinary Cancers Symposium.[155] MDRT added to ADT and enzalutamide in oligometastatic CRPC (with 1–5 metastases) led to improvements in radiologic PFS, biochemical PFS, and time to next line of therapy compared with ADT with enzalutamide alone.

The panel includes MDT with mCRPC systemic therapy as an option for patients with oligometastatic or oligoprogressive CRPC regardless of prior therapy.

Small Cell/Neuroendocrine Prostate Cancer

De novo small cell carcinoma in untreated prostate cancer occurs rarely and is very aggressive.[156] Treatment-associated small cell prostate cancer/ neuroendocrine prostate cancer that occurs in patients with mCRPC is more common.[157] 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% of patients.[157] 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.[158] 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; Figure 6).[96,159,160] 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.[161] 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; $P=.01$).[162] No significant differences were found in OS. Other bisphosphonates have

not been shown to be effective for prevention of disease-related skeletal complications.

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-metastatic CRPC treated with docetaxel alone or with zoledronic acid, 89Sr, or both.[163] 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=.03). For secondary outcomes, zoledronic acid improved the SRE-free interval (HR, 0.78; 95% CI, 0.65–0.95; P=.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.[164] The absolute incidence of SREs was similar in the two 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 noninferiority; P=.008 for superiority). The rates of important SREs with denosumab were similar to zoledronic acid and included spinal cord compression (3% vs 4%), need for radiation (19% vs 21%), and pathologic fracture (14% vs 15%). Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs 6%), arthralgias, and osteonecrosis of the jaw (1%–2% incidence).

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.[165] In the every-12-week and every-4-week arms, 28.6% and 29.5% experienced at least 1 SRE within 2 years of randomization, respectively.

Use of zoledronic acid in patients with CSPC and bone metastases is not associated with lower risk for SREs.[166] Therefore, the routine use of these agents in bone-metastatic CSPC is not recommended. Bone antiresorptive agents should, however, be used for SRE prevention in patients with CSPC if they have treatment-related bone loss (see "Principles of Survivorship, Bone Health in Prostate Cancer," in the algorithm [available at NCCN.org]).

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.[167] Most, but not all, patients who develop osteonecrosis of the jaw have preexisting dental problems.[168] 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.[66] 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 in patients with mCRPC without visceral metastases (see previous section on "Radium-223"). The use of palliative RT 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.[169] 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, there are fewer data on treatment of patients with CRPC and visceral metastases than for those without visceral metastases.

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 that can help with treatment selection in some cases continues to emerge.

After abiraterone or enzalutamide, data suggest that giving the alternate ARPI 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).[90] Furthermore, data suggest cross-resistance between abiraterone and enzalutamide.[170–173] Results of a randomized, open-label, phase II, crossover trial suggest that the sequence of abiraterone followed by enzalutamide may be more efficacious than the reverse.[174]

Some data inform the sequencing of therapies in patients with PSMA-positive mCRPC. The multicenter, unblinded, randomized phase II TheraP trial compared PSA response after Lu-177-PSMA-617 versus cabazitaxel in 200 patients with PSMA-positive mCRPC who previously received docetaxel.[175] 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 who 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 as discussed previously (see "Lutetium Lu 177 Vipivotide Tetraxetan") showed that Lu-177-PSMA-617 improved

rPFS compared with switching to a different ARPI in docetaxel-naïve patients.[146]

Data for patients with HRRm mCRPC are more limited, but comparative effectiveness research suggests that olaparib may result in superior radiographic PFS than cabazitaxel in patients with *BRCA1* or *BRCA2* mutations and prior treatment with docetaxel.[176] Furthermore, data from PROfound and TRITON3 suggest that a PARP inhibitor is preferred over a different ARPI in patients with BRCAm mCRPC and prior ARPI exposure.[129,133]

No chemotherapy regimen has demonstrated improved survival or QOL after cabazitaxel or cabazitaxel/carboplatin in patients with mCRPC of adenocarcinoma histology, although several systemic agents other than mitoxantrone have shown palliative and radiographic response benefits in clinical trials (ie, carboplatin, cyclophosphamide, doxorubicin, vinorelbine, carboplatin/etoposide, docetaxel/carboplatin, gemcitabine/oxaliplatin, paclitaxel/carboplatin).[177–186] No survival benefit for any 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. In patients not able to receive life prolonging therapy, prednisone and dexamethasone at low doses may provide palliative benefits.[187] 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 limited 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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