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Release date: December 10, 2022; Expiration date: December 10, 2023

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Prostate Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Prostate Cancer

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

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The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.
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The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

Edward M. Schaeffer, MD, PhD, Panel Chair, has disclosed serving as a scientific advisor for AbbVie, Inc., Astellas Pharma US, Inc., Janssen Scientific Affairs, LLC, Lantheus, and Pfizer, Inc.
Sandy Srinivas, MD, Panel Vice Chair, has disclosed serving as a scientific advisor for Bayer HealthCare, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., and Novartis Pharmaceuticals Corporation; and receiving grant/research support from Bayer HealthCare, Merck & Co., Inc., and Novartis Pharmaceuticals Corporation.
Brian Chapin, MD, Panel Member, has disclosed serving as a scientific advisor for Janssen Pharmaceutica Products, LP, Merck & Co., Inc., and Pfizer Inc.; receiving grant/research support from Blue Earth Diagnostics and Regeneron Pharmaceuticals, Inc.; and receiving consulting fees from Johnson & Johnson.
Rana R. McKay, MD, Panel Member, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, AVEO Pharmaceuticals, Inc., Bayer HealthCare, Bristol-Myers Squibb Company, Calithera Biosciences Inc., Caris Life Sciences, Dendreon Corporation, Exelixis Inc., Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Myovant Sciences, Novartis Pharmaceuticals Corporation, Pfizer Inc., sanofi-aventis US, SeaGen, Sorrento Therapeutics, Inc., Telix Pharmaceuticals Limited, and Tempus Labs, Inc.; and receiving grant/research support from Bayer HealthCare.
Daniel Spratt, MD, Panel Member, has disclosed receiving honorarium from Blue Earth Diagnostics, Novartis Pharmaceuticals Corporation, Pfizer Inc., and Varian Medical Systems, Inc.; and receiving consulting fees from Bayer HealthCare.
Benjamin A. Teply, MD, Panel Member, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Hospicom Inc., sanofi-aventis U.S., and SeaGen; receiving grant/research support from Bellicum Pharmaceuticals, Inc., Bristol-Myers Squibb Company, and QED Pharmaceutical Services, LLC; and serving as a scientific advisor for Pfizer Inc.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

This activity is supported by educational grants from AstraZeneca; BeiGene; Exact Sciences; Gilead Sciences, Inc.; GlaxoSmithKline; Lantheus Medical Imaging Inc.; Novartis; Pharmacyclics LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Astellas. This activity is supported by an education grant from Astellas and Seagen Inc. This activity is supported by a medical education grant from Karyopharm® Therapeutics. This activity is supported through an Independent Medical Education grant from Merck & Co., Inc.

Prostate Cancer, Version 1.2023

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Prostate Cancer address staging and risk assessment after a prostate cancer diagnosis and include management options for localized, regional, recurrent, and metastatic disease. The NCCN Prostate Cancer Panel meets annually to reevaluate and update their recommendations based on new clinical data and input from within NCCN Member Institutions and from external entities. These NCCN Guidelines Insights summarizes much of the panel's discussions for the 4.2022 and 1.2023 updates to the guidelines regarding systemic therapy for metastatic prostate cancer.

J Natl Compr Canc Netw 2022;20(12):1288–1298
doi: 10.6004/jnccn.2022.0063

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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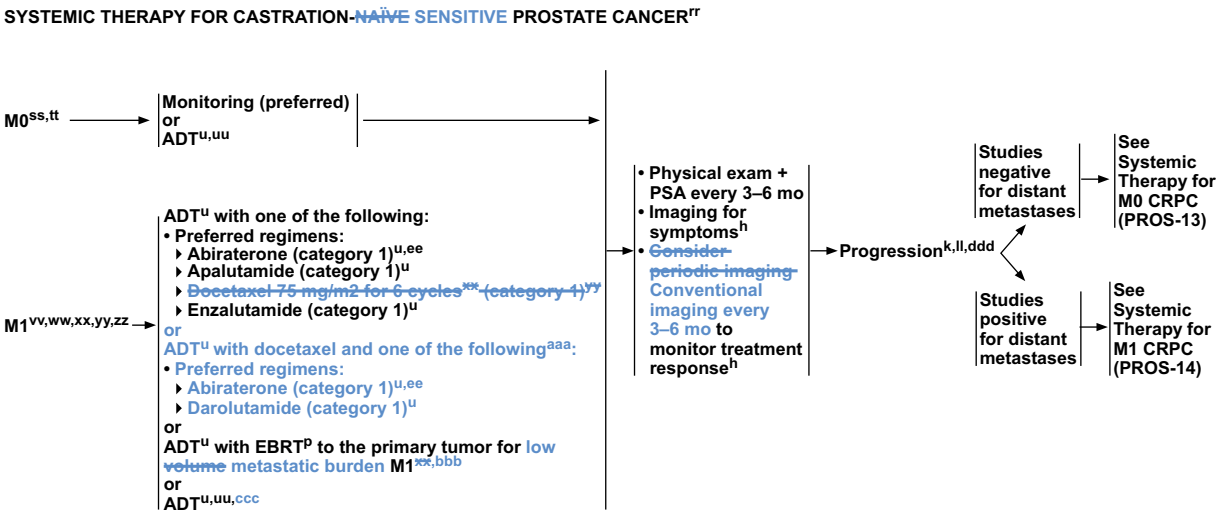

See footnotes on PROS-12A

Overview

Localized prostate cancer represents a spectrum of disease, ranging from indolent disease that may not require treatment (ie, active surveillance or observation) to disease that requires some treatment (eg, radical prostatectomy or radiation) to aggressive disease that requires intensive treatment (eg, radical prostatectomy with adjuvant therapy or radiation with androgen deprivation therapy [ADT]).[1]

Some patients with prostate cancer have metastatic disease at initial diagnosis or patients may develop metastases after initial therapy without long-term ADT. These patients have metastatic castration-sensitive prostate cancer (CSPC). The term *castration-sensitive* is used to define patients who have not been treated with ADT or those who are not on ADT at the time of progression. ADT with treatment intensification is the preferred approach for most patients with metastatic CSPC. In most cases, the disease eventually stops responding to ADT and is categorized as *castration-resistant*.[2] For metastatic castration-resistant prostate cancer (CRPC), ADT is continued while additional systemic therapies are sequentially applied.[1]

Systemic Therapy for Metastatic Castration-Sensitive Disease

ADT with systemic treatment intensification is strongly recommended for most patients with metastatic CSPC. Preferred options in the previous version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer in this setting were ADT with either abiraterone, apalutamide, docetaxel, or enzalutamide. These doublet therapies were all included as category 1 recommendations and were preferred for most patients. An additional option is ADT with localized treatment intensification with external-beam radiation therapy (EBRT) to the primary tumor for low-volume metastatic disease. ADT alone is generally only used for patients who are unable to tolerate intensive therapy.

ADT With Docetaxel and Novel Hormone Therapy

Several panel members requested that the panel consider the addition of triplet therapies of ADT with docetaxel and a novel hormone therapy—either abiraterone or darolutamide—based on results of the PEACE-1 and ARASENS trials (discussed in the following sections).[3,4] Both trials showed an overall survival (OS) benefit of

[h] See Principles of Imaging (PROS-E).
[k] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.
[p] See Principles of Radiation Therapy (PROS-G).
[u] See Principles of Androgen Deprivation Therapy (PROS-I).
[ee] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).
[ll] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).
[rr] The term "castration-~~naïve~~ sensitive" is used to define patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-~~naïve~~ sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[ss] PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.
[tt] Patients with a life expectancy ≤5 years can consider observation. See Principles of Active Surveillance and Observation (PROS-F).
[uu] Intermittent ADT can be considered for patients with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-I).
[vv] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[ww] ADT alone (see PROS-I) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.
[xx] Tumor and germline testing for homologous recombination repair gene mutations (HRRm) is recommended and tumor testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR) can be considered. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
~~[xx] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis-vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.~~
~~[yy] See Principles of Non-Hormonal Systemic Therapy (PROS-J).~~
[yy] Stereotactic body RT (SBRT) to metastases can be considered in patients with oligometastatic progression where progression-free survival (PFS) is the goal.
[zz] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-I.
[aaa] The panel encourages ADT with docetaxel and either darolutamide or abiraterone for patients with high-volume disease who are fit for chemotherapy. See Principles of Non-Hormonal Systemic Therapy (PROS-J).
[bbb] EBRT to the primary tumor is associated with an overall survival benefit in patients with low metastatic burden at the time of diagnosis of metastatic disease, which is defined by conventional imaging as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis (Ali A, et al. JAMA Oncol 2021;7:555-563). See Principles of Radiation Therapy (PROS-G).
[ccc] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy.
[ddd] Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-sensitive disease.

PROS-12A

triplet therapy over ADT with docetaxel. The panel voted unanimously to include both of these treatments as category 1, preferred options for patients with metastatic CSPC (see PROS-12, page 1290). In addition, the panel added a footnote stating that they encourage use of ADT with docetaxel and either darolutamide or abiraterone for patients with high-volume disease who are fit for chemotherapy (see PROS-12A, above).

ADT With Docetaxel and Abiraterone

PEACE-1 was an international, open-label, randomized, phase III study conducted in 7 European countries.[3] 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 radiation therapy, standard of care with abiraterone, or standard of care with radiation and abiraterone. The 2 primary endpoints of the trial were radiographic progression-free survival (PFS) and OS. Adjusted Cox regression modeling showed no interaction between abiraterone and radiation therapy, so data were pooled for the analysis of abiraterone efficacy. Consistent with results of older studies, radiographic PFS was longer in patients who received abiraterone than in those who did not (hazard ratio [HR], 0.54; 99.9% CI, 0.41–0.71; $P<.0001$) as was OS (HR, 082; 95.1% CI, 0.69–0.98; $P=.030$).

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

ADT With Docetaxel and Darolutamide

The international phase III ARASENS trial, the second phase III trial evaluating a triplet, randomized 1,306 patients with metastatic CSPC to receive ADT and docetaxel with either darolutamide or matching placebo.[4] The primary end point, OS, was improved in the darolutamide group at 4 years (62.7%; 95% CI, 58.7–66.7) compared with the placebo group (50.4%; 95% CI, 46.3–54.6). The risk of death was lower in the darolutamide group by approximately 32% (HR, 0.68; 95% CI, 0.57–0.80; $P<.001$).

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,sss]
• Preferred regimens ▸ Abiraterone[u,nnn] (category 1[ooo]) ▸ Docetaxel[fff,ppp] (category 1) ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Preferred regimens ▸ Docetaxel (category 1)[fff] ▸ ~~Sipuleucel-T[fff,qqq]~~ • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Olaparib for HRRm (category 1)[ttt] ▸ ~~Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]~~ ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCAm[uuu] ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Abiraterone + dexamethasone[nnn,vvv] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm]	**Prior docetaxel and prior novel hormone therapy[mmm,sss]**
• Preferred regimens ▸ Abiraterone[u,nnn] (category 1) ▸ Cabazitaxel[fff] ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ ~~Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]~~ ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ ~~Sipuleucel-T[fff,qqq]~~ ▸ Other secondary hormone therapy[u]	• Useful in certain circumstances ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[www] (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[fff] (category 1[ooo]) ▸ Docetaxel rechallenge[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Olaparib for HRRm (category 1[ooo])[ttt] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1[ooo]) ▸ Rucaparib for BRCAm[uuu] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]

See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

PROS-15

The addition of darolutamide also showed significant benefits over placebo for secondary efficacy end points, including time to CRPC (HR, 0.36; 95% CI, 0.30–0.42; $P<.001$), 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; $P<.001$).

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

ADT With Docetaxel and Enzalutamide

A panel member asked the panel whether the guidelines should include triplet therapy with ADT, docetaxel, and enzalutamide in the metastatic castration-sensitive setting based on the fact that that approximately 43% of patients in ENZAMET received triplet therapy.[5] However, other panel members pointed out that only approximately 30% received the full planned 6 cycles of docetaxel and that the HR for OS in the subset of patients with planned docetaxel did not reach significance (HR, 0.90; 95% CI, 0.62–1.31). The panel agreed that this result is likely because the trial was underpowered to address the benefit of triplet compared with doublet therapy. Overall, the panel does not believe that evidence of benefit for enzalutamide with docetaxel and ADT in this setting reaches the strength of evidence available for abiraterone and darolutamide. In addition, adverse events—notably grade 2/3 peripheral sensory neuropathy—were more common with the addition of docetaxel. The panel consensus was to omit this option until more data are available.

ADT With Docetaxel

A panel member proposed that ADT with docetaxel as doublet therapy should be removed as an option from the guidelines, stating that if docetaxel is given, it should be given with abiraterone or darolutamide. Some panel members argued against its removal, wanting to keep it as an option for patients who have concerns about the adverse effects or costs of novel hormonal therapies or

FOOTNOTES

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

[fff] See Principles of Non-Hormonal Systemic Therapy (PROS-J).

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

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

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

[lll] Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

[mmm] Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. ~~received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC~~ Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.

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

[ooo] The noted category applies only if there are no visceral metastases.

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

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

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

[sss] Consider AR-V7 testing to help guide selection of therapy (See Discussion).

[ttt] Olaparib is a treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC) and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*) who have been treated previously with androgen receptor-directed therapy. However, efficacy appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis. There may be heterogeneity of response to olaparib for non-*BRCA* mutations based on the specific gene mutation. (See Discussion).

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

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

[www] 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. The panel believes that both Ga-68 PSMA-11 or F-18 piflufolastat PSMA imaging can be used to determine eligibility. Sartor et al. N Engl J Med 2021; 385:1091-1103. See Principles of Radiation Therapy (PROS-G).

PROS-15A

for cases in which there may be concerns about the patient taking the novel hormonal treatment as recommended. Others pointed out that there are phase III data showing ADT with docetaxel has a survival benefit over ADT alone, which remains an option in the guidelines for patients with clear contraindications to combination therapy. However, the panel voted to remove this doublet option because the triplet options of ADT with docetaxel and either abiraterone or darolutamide showed improved OS over ADT with docetaxel (see PROS-12, page 1290).

ADT With EBRT to the Primary Tumor

The STAMPEDE Arm H randomized trial and a subsequent meta-analysis that combined data from STAMPEDE Arm H with data from the HORRAD randomized trial demonstrated that men with low-volume disease had an OS benefit from the addition of EBRT to ADT with or without docetaxel.[6,7] Subsequent post hoc analyses identified an OS benefit for patients with up to 4 bone metastases, and a failure-free survival benefit for patients with up to 9 bone metastases.[8] Metastatic burden in these trials was assessed using conventional imaging (CT and bone scan) and not molecular PET imaging or total-body MRI. One panel member noted that it is probable that a higher burden of disease would be detected using newer, more sensitive imaging agents and thus that treatment of the primary tumor should be based on disease detected by conventional imaging, and not excluded solely based on advanced imaging findings. Based on these results, ADT with EBRT to the primary tumor is included in the guidelines an option for patients with low metastatic burden at the time of diagnosis (defined by conventional imaging as either nonregional, lymph-node-only disease or <4 bone metastases and without visceral/other metastasis) (see PROS-12, page 1290). Importantly, STAMPEDE used reduced doses of EBRT, which resulted in no significant increase in toxicity, and dose-escalated EBRT or brachytherapy is not recommended in this setting.

Some panel members questioned whether it would be reasonable to include an androgen receptor–directed therapy in combination with ADT + EBRT to the primary tumor. They noted that (1) the benefit of EBRT to the primary tumor in STAMPEDE was similar between 82% of patients who received ADT without docetaxel and the 18% of patients who received docetaxel in a prespecified analysis, and (2) the addition of docetaxel or abiraterone to ADT resulted in comparable survival benefits in STAMPEDE.[6,9] Overall, however, most panel members believe it is unclear whether the use of secondary hormonal therapies with

PRINCIPLES OF RADIATION THERAPY

Radiopharmaceutical Therapy

- **Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in patients with visceral metastases or bulky nodal disease (>3–4 cm). Radium-223 differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (ie, 2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.**
- **Radium-223 is administered IV once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.**
- **Prior to the initial dose, patients must have absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10 g/dL.**
- **Prior to subsequent doses, patients must have ANC ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label). Radium-223 should be discontinued if a delay of 6–8 weeks does not result in the return of blood counts to these levels.**
- **Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.**
- **Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except in a clinical trial.**
- **Radium-223 may increase fracture risk when given concomitantly with abiraterone.**
- **Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT.**
- **Concomitant use of denosumab or zoledronic acid is recommended; it does not interfere with the beneficial effects of radium-223 on survival.**
- **Lu-177–PSMA-617**
  - **Lu-177–PSMA-617 is a beta-emitting radiopharmaceutical that selectively binds to PSMA receptors on prostate cancer cells. In patients with PSMA-positive disease, Lu-177–PSMA-617 has been shown to improve overall survival in patients with progressive mCRPC previously treated with androgen receptor inhibitors and taxane chemotherapy. Sartor O, et al. N Engl J Med 2021;385:1091-1103.**
  - **Lu-177–PSMA-617 is not recommended in patients with dominant PSMA-negative lesions. PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥1.0 cm, lymph nodes ≥2.5 cm in short axis, and solid organ metastases ≥1.0 cm in size.**
  - **Lu-177–PSMA-617 is typically administered IV 200 mCi (7.4 GBq) every 6 weeks for a total of 6 treatments by an appropriately licensed facility, usually in nuclear medicine or RT departments. Patients should be well-hydrated during treatment. Because Lu-177 also emits gamma radiation, appropriate precautions should be taken to minimize exposure to personnel administering the radiopharmaceutical. Treatment rooms should be monitored for potential contamination following treatments, and patients should be provided written instructions regarding radiation safety precautions following treatment.**
  - **The most frequently reported side effects from Lu-177–PSMA-617 include fatigue (43%), dry mouth (39%), nausea (35%), and anemia (32%).**
  - **Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177–PSMA-617, the panel believes that F-18 piflufolastat PSMA can also be used in the same space due to multiple reports describing the equivalency of the two imaging agents in:**
    - ◊ **PSMA molecular recognition motifs,**
    - ◊ **normal organ biodistribution, and**
    - ◊ **detection accuracy of prostate cancer lesions.**

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EBRT to the primary tumor is appropriate for patients with metastatic CSPC. Panel members noted that the effects of combining ADT with local therapy and secondary hormone therapy are being further evaluated in the PEACE-1 trial (EBRT to the primary tumor with abiraterone) and the S1802 trial (radical prostatectomy or EBRT to the primary tumor with any standard systemic therapy based on NCCN Guidelines for Prostate Cancer; ClinicalTrials.gov identifier: NCT03678025).[3] Given that secondary hormone therapy adds toxicity and cost and an unclear benefit, the panel consensus was to await results from these trials before considering adding such combinations to the guidelines.

Systemic Therapy for Metastatic CRPC

Most advanced prostate cancer eventually stops responding to ADT and is then categorized as castration-resistant. CRPC is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).[2]

For patients who develop metastatic CRPC, ADT is continued to maintain castrate serum levels of testosterone (<50 ng/dL) while additional systemic therapies are applied in a sequential fashion. For patients with bone metastases and CRPC, the addition of bone-modifying drugs is recommended in addition to antineoplastic therapy. Systemic therapies for metastatic CRPC include various secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, based on a large body of data. Choice of treatments in various lines of therapy is based on patient preferences, prior treatment exposures, the presence or absence of visceral disease and certain biomarkers, patient symptoms, and potential adverse effects.

Lutetium Lu 177 Vipivotide Tetraxetan

Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) is an intravenously administered radiopharmaceutical that is indicated for prostate-specific membrane antigen (PSMA)–positive metastatic CRPC that has been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.[10] The active moiety is a radionuclide that delivers radiation to PSMA-expressing and surrounding cells, inducing DNA damage and leading to cell death.[10] FDA approval of Lu-177-PSMA-617 in March 2022 was based on the international, open-label phase III VISION trial of 831 patients with metastatic CRPC and PSMA-positive metastatic lesions.[10,11] Patients were previously treated with at least one androgen receptor–directed therapy and 1 or 2 taxane-based chemotherapy regimens. Patients had at least one PSMA-positive metastatic lesion and

no PSMA-negative lesions, as determined by gallium-68 (Ga-68)–labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard care (abiraterone, enzalutamide, bisphosphonates, radiation therapy, denosumab, and/or glucocorticoids) and Lu-177-PSMA-617 (7.4 GBq or 200 mCi every 6 weeks for 4–6 cycles) or standard care alone.[11]

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.[11]

The panel discussed the data and voted unanimously to include Lu-177-PSMA-617 as a category 1 option in the guidelines 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 (see PROS-15, PROS-15A, and PROS-G 6 of 7, pages 1292, 1293, and 1294, respectively). One panel member suggested that Lu-177-PSMA-617 should also be an option for patients prior to receipt of docetaxel chemotherapy if they are not candidates for docetaxel. However, the panel voted to align the guideline recommendation with the population in VISION. The panel discussed whether Lu-177-PSMA-617 should be a category 1 recommendation regardless of visceral metastases; all other systemic therapies in this setting have been designated as category 2B recommendations if visceral metastases are present. The panel noted that 22% of the analysis set in the VISION trial had lung or liver metastases.[11] They therefore agreed that the category 1 designation for Lu-177-PSMA-617 could be for all patients with metastatic CRPC who received prior docetaxel and prior novel hormonal therapy.

The panel next discussed what imaging studies could be used to define PSMA-positive lesions. The VISION study used Ga-68 PSMA-11 PET/CT, but several panel members noted that all approved PSMA PET imaging agents should be acceptable. The panel discussed the fact that the 2 FDA approved PSMA imaging agents—Ga68-PSMA-11 and F-18 piflufolastat PSMA—share the same PSMA binding motif with each other and with Lu-177-PSMA-617. The 2 agents also have similar biodistribution patterns.[12,13] Furthermore, a growing body of evidence suggests that they have a similar ability to detect prostate cancer.[14–17] Based on these data and because of the limited availability Ga-68 PSMA-11, the panel decided that both Ga-68 PSMA-11 and F-18 piflufolastat PSMA imaging should be options for determining eligibility for Lu-177-PSMA-617 (see PROS-15A and PROS-G 6 of 7, pages 1293 and 1294, respectively).

Abiraterone With Olaparib

Early studies suggest germline and somatic mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*) may be predictive of the clinical benefit of PARP inhibitors.[18–20] PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.[21] Currently, 2 PARP inhibitors—olaparib and rucaparib—are approved by the FDA for use in prostate cancer.[22,23] Both of these agents are recommended as options for appropriate patients with metastatic CRPC in the NCCN Guidelines (see PROS-15, page 1292).

The panel received an external request to include olaparib + abiraterone as a combination treatment option with continued ADT for patients with metastatic CRPC, irrespective of HRR gene biomarker status. This request is based on results from the phase III PROpel trial and a separate phase II study.[20,24,25] The phase II study was an international, randomized, double-blind, placebo-controlled trial that included 142 patients with metastatic CRPC and previous docetaxel who were candidates for abiraterone treatment.[20] All patients received abiraterone and were randomized to also receive olaparib or placebo, regardless of HRR mutation status. The primary endpoint of radiographic PFS was longer in the olaparib group than in the placebo group (13.8 vs 8.2 months; HR, 0.65; 95% CI, 0.44–0.97; $P=.034$). The frequency of grade ≥3 adverse events was greater in the olaparib group (54% vs 28%), including anemia, pneumonia, and myocardial infarction. Exploratory analysis of this phase II study showed that radiographic PFS was improved with the addition of olaparib in the group of patients without HRR mutations (HR, 0.54; 95% CI, 0.32–0.93) and in those with HRR mutations (HR, 0.62; 95% CI, 0.23–1.65).[25]

In the double-blind, phase III PROpel trial, the benefit of adding olaparib to abiraterone was tested in the first-line metastatic CRPC setting, again regardless of HRR mutation status.[24] The primary end point of imaging-based PFS was longer in the olaparib group at the time of prespecified primary analysis (24.8 vs 16.6 months; HR, 0.66; 95% CI, 0.54–0.81; $P<.001$). Anemia, the most common grade ≥3 adverse event, occurred in 15.1% of patients who received olaparib and 3.3% of those in the placebo group. Pulmonary embolism occurred in 6.5% and 1.8% of patients in the olaparib and placebo arms, respectively. Other adverse events occurred at similar frequencies between the 2 groups. OS is a secondary endpoint of the trial, but the data are not yet mature for this analysis.

The panel discussed the data from these trials and whether it would be reasonable to include abiraterone + olaparib with continued ADT as an option for patients

with metastatic CRPC in the setting of no prior novel hormone therapy based on the results. A panel member noted that patients would have to be fit enough for olaparib and willing to accept the added cost and toxicity, knowing that the OS data are immature.

A panel member brought up the MAGNITUDE trial, results of which were presented at the 2022 ASCO Genitourinary Cancers Symposium.[26] MAGNITUDE was similar in design to PROpel, and examined the efficacy of another PARP inhibitor, niraparib, in combination with abiraterone in first-line metastatic CRPC. In this trial, the addition of niraparib only resulted in a radiographic PFS benefit in the population with mutations in an HRR gene. The lower starting dose of niraparib in this trial may have been an issue; however, the inconsistency between results of MAGNITUDE and PROpel trials was concerning to some.

The panel also discussed whether using radiographic PFS as an endpoint was appropriate. The panel had not used this endpoint in the past for this setting, and the OS data on the olaparib/abiraterone combination are not yet mature. Some panel members noted that radiographic PFS might be acceptable to consider for patients with higher-risk disease, such as those with a *BRCA1* or *BRCA2* mutation. Other panel members noted that radiographic PFS is unlikely to be a good surrogate for OS.

Several panel members expressed concerns over the lack of data showing that giving olaparib and abiraterone in combination is any better than giving them sequentially, which has been an option in the guidelines for several years. If the 2 agents are not acting synergistically, then OS is likely to be the same if they are given sequentially. The panel noted that results of the BRCAAWAY trial will be able to answer this question more definitively in the future.[27] In this phase II trial, patients with *BRCA1*, *BRCA2*, and/or *ATM* mutations are randomized to receive abiraterone alone, olaparib alone, or abiraterone in combination with olaparib. The patients receiving either agent alone are allowed to crossover to the other agent at progression.

Considering the immaturity of the OS data, the lack of evidence for benefit of giving the drugs in combination rather than sequentially, inconsistency across trials, and the added toxicity of the combination, the panel members unanimously agreed to exclude this combination from the guidelines at this time. As one panel member noted, they are obligated to "first do no harm." It was also noted that its omission is unlikely to impact many patients, because most patients in current times have novel hormone therapy in the castration-sensitive setting and would therefore not be eligible for the combination therapy in the CRPC setting.

Pembrolizumab

Pembrolizumab is an anti–PD-1 antibody that has been studied extensively in advanced colorectal cancer and several other cancers. Data in metastatic CRPC are more limited.[28–34]

The panel reviewed a suggestion from an NCCN Member Institution to align the recommendations for pembrolizumab with the FDA label. In the 2022 and previous versions of NCCN Guidelines, it was included as an option for patients with metastatic CRPC and microsatellite instability–high (MSI-H) status, mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) ≥10 mut/Mb and prior treatment with a novel hormone therapy and/or docetaxel. The FDA label states that pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, MSI-H, dMMR, or TMB-high solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[35] Given the limited data on the efficacy of pembrolizumab specifically in prostate cancer, the panel members agree unanimously that it should not be included in the guidelines as an option to be given before other treatment choices, many of which are included as category 1 options. It was therefore removed for as an option for patients who have not yet had docetaxel and a novel hormone therapy (see PROS-15, page 1292). It is still included as an option for patients with metastatic CRPC who have received prior docetaxel and a prior novel hormonal therapy.

Other Systemic Therapy Options Considered by the Panel

The panel received external submissions to consider several other systemic therapy options for patients with metastatic CRPC. The panel reviewed the data for all of them (discussed in the following sections) and voted unanimously in each case that the data were insufficient for inclusion in the NCCN Guidelines at this time.

Darolutamide

The panel discussed the external request to consider including darolutamide as an option for the treatment of metastatic CRPC. This androgen receptor inhibitor has been studied in the CRPC setting in the phase II ODENZA study. Results of this prospective, randomized, open-label, crossover study, which was performed among several institutions in France, were presented at the 2021 ASCO Annual Meeting.[36] Patients were randomized to receive darolutamide for 12 weeks followed by enzalutamide for 12 weeks or the reverse sequence. The primary endpoint was patient preference between the 2 agents at 24 weeks. A nonsignificantly higher number of patients preferred darolutamide over enzalutamide, potentially because of less fatigue.

Earlier, company-sponsored phase I and I/II trials for darolutamide in the metastatic CRPC setting show some promise for the use of darolutamide in this setting, but the panel deems the data insufficient at this time.[37–39]

Talazoparib

The panel received an external request to consider the inclusion of talazoparib as an option for the treatment of patients with metastatic CRPC and HRR gene mutations who were previously treated with taxane-based chemotherapy and a novel hormonal. Talazoparib is a PARP inhibitor with an FDA indication in breast cancer.[40] This request was based on results of the open-label, international phase II TALAPRO-1 trial.[41] The trial included 127 patients with an HRR mutation and progressive, metastatic CRPC, all of whom received at least one dose of talazoparib. 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%). The panel awaits more evidence, such as from the ongoing TALAPRO-2 study, which is comparing enzalutamide with either talazoparib or placebo in untreated patients with metastatic CRPC (ClinicalTrials.gov identifier: NCT03395197).[42] The coprimary endpoints of TALAPRO-2 are radiographic PFS in all patients and radiographic PFS in patients with HRR mutations.

Nivolumab With Ipilimumab

Another external request the panel received was to consider including the immunotherapy combination of nivolumab and ipilimumab as a treatment option for patients with TMB-high metastatic CRPC whose disease is refractory to standard therapies or who have no standard treatment options available. This request was based on results of the CheckMate 848 trial presented at the American Association for Cancer Research 2022 Meeting.[43] This trial assessed the use of nivolumab with ipilimumab for the treatment of progressive advanced or metastatic solid TMB-high tumors. Panel members noted that the trial included few if any patients with prostate cancer. Previous studies of this combination in patients with metastatic CRPC showed that it has limited efficacy and considerable toxicity.[44,45] The panel concluded that the data were insufficient for inclusion of this combination in the NCCN Guidelines.

Conclusions

Systemic therapy options for patients with metastatic CSPC and CRPC continue to evolve. The NCCN Guidelines for Prostate Cancer now include triplet therapy with ADT, docetaxel, and 1 of 2 secondary hormone therapies (abiraterone or darolutamide) for the treatment of metastatic castration-sensitive disease. The panel encourages use of these triplet options for patients with high-volume disease who are fit for chemotherapy. In the metastatic CRPC setting, the guidelines now include the radiopharmaceutical Lu-177-PSMA-617 as an option for patients with PSMA-positive disease. Ongoing clinical trials are addressing possible future advances in the treatment of metastatic prostate cancer.

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