

Prostate Cancer, Version 2.2019

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ABSTRACT

The NCCN Guidelines for Prostate Cancer include recommendations regarding diagnosis, risk stratification and workup, treatment options for localized disease, and management of recurrent and advanced disease for clinicians who treat patients with prostate cancer. The portions of the guidelines included herein focus on the roles of germline and somatic genetic testing, risk stratification with nomograms and tumor multigene molecular testing, androgen deprivation therapy, secondary hormonal therapy, chemotherapy, and immunotherapy in patients with prostate cancer.

J Natl Compr Canc Netw 2019;17(5):479–505
doi: 10.6004/jnccn.2019.0023

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.

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Disclosures for the NCCN Prostate Cancer Panel

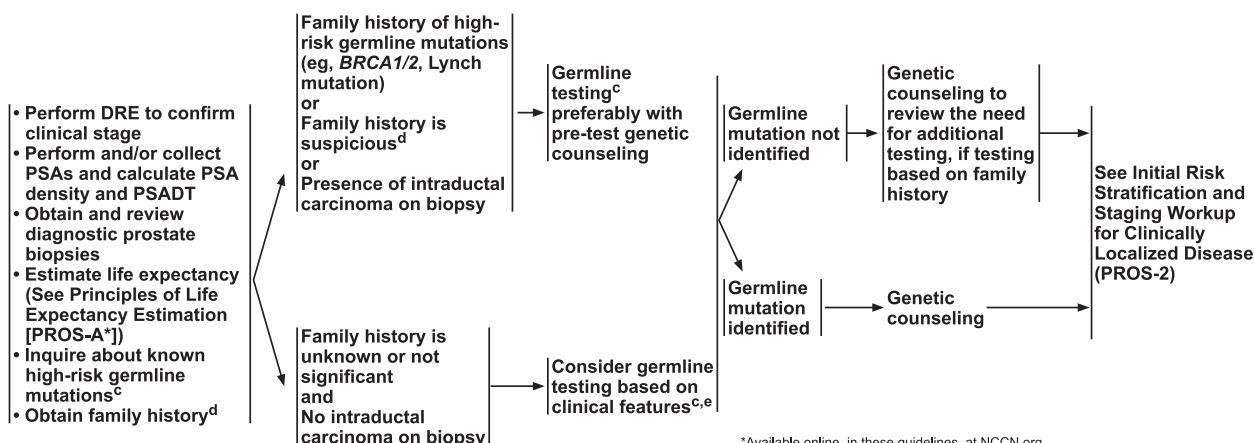
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Individual disclosures for the NCCN Prostate Cancer Panel members can be found on page 505. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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INITIAL PROSTATE CANCER DIAGNOSIS^{a,b}

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^a See NCCN Guidelines for Older Adult Oncology[†] for tools to aid optimal assessment and management of older adults.^b See NCCN Guidelines for Prostate Cancer Early Detection.[†]^c Family history for known germline variants and genetic testing for germline variants should include *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *CHEK2*. Consider cancer predisposition next-generation sequencing (NGS) panel testing, which includes *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Additional genes may be appropriate depending on clinical context. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease, but testing may be valuable for family counseling.^d Family history criteria and consideration to prompt genetic testing:

- ▶ A strong family history of prostate cancer consists of: brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at less than 60 years of age or who died from prostate cancer
- ▶ Ashkenazi Jewish ancestry
- ▶ ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer

^e Genetic testing in the absence of family history or clinical features (eg, high- or very-high-risk prostate cancer, intraductal histology) may be of low yield. The patient should be counseled to inform providers of any update to family history.

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PROS-1

Overview

An estimated 174,650 new cases of prostate cancer will be diagnosed in 2019, accounting for 20% of new cancer cases in men.¹ The age-adjusted death rates from prostate cancer have declined 51% from 1993 to 2016.¹ Researchers have estimated that prostate cancer will account for 9.8% of male cancer deaths in 2018.¹ Over the past several years, the incidence of prostate cancer has declined, likely in part as a result of decreased detection attributed to decreased rates of prostate-specific antigen (PSA) screening.^{2–4} The decreasing and comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer.

Early detection can lead to overtreatment of prostate cancers that do not threaten life expectancy, which results in unnecessary side effects that impair quality of life (QOL) and increase health care expenditures. The U.S. Preventive Services Task Force (USPSTF) recommended against PSA testing in 2012.⁵ The incidence of metastatic disease has increased.^{4,6} The rate of prostate cancer mortality, which had been in decline for 2 decades, has stabilized.⁴ Prostate cancer incidence and deaths have increased in the past few years for the first time in recent

history, with prostate cancer deaths increasing from an estimated 26,730 in 2017 to 31,620 in 2019.^{1,7} Increases in the incidence of metastases at presentation and in prostate cancer deaths may be influenced by declines in the rates of prostate cancer early detection, biopsies, diagnosis of localized prostate cancers, and radical prostatectomy that followed the 2012 USPSTF recommendations.^{8–18} The USPSTF released updated recommendations in 2018 that include individualized, informed decision-making regarding prostate cancer screening in men aged 55 to 69 years.¹⁹ These updated recommendations may allow for a more balanced approach to prostate cancer early detection. Better use of PSA for early detection of potentially fatal prostate cancer (see the NCCN Guidelines for Prostate Cancer Early Detection, available at NCCN.org) should decrease the risk of overdetection and overtreatment AND preserve the decrease in prostate cancer mortality.

Prostate Cancer Genetics

Family history of prostate cancer raises the risk of prostate cancer.^{20–22} In addition, prostate cancer has been associated with hereditary breast and ovarian cancer (HBOC) syndrome (due to germline mutations in

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk group	Clinical/pathologic features			Imaging ^{h,i}	Germline testing	Molecular and biomarker analysis of tumor ^l	Initial therapy
Very low ^f	<ul style="list-style-type: none">• T1c AND• Grade Group 1 AND• PSA <10 ng/mL AND• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core^g AND• PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Not indicated	See PROS-4*
Low ^f	<ul style="list-style-type: none">• T1-T2a AND• Grade Group 1 AND• PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y ^m	See PROS-5*
Intermediate ^f	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): <ul style="list-style-type: none">• T2b-T2c• Grade Group 2 or 3• PSA 10–20 ng/mL	Favorable intermediate	<ul style="list-style-type: none">• 1 IRF and• Grade Group 1 or 2 and• <50% biopsy cores positive^g	<ul style="list-style-type: none">• Bone imaging^j: not recommended for staging• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement• <u>If regional or distant metastases are found</u>, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y ^m	See PROS-6*
		Unfavorable intermediate	<ul style="list-style-type: none">• 2 or 3 IRFs and/or• Grade Group 3 and/or• ≥50% biopsy cores positive^g	<ul style="list-style-type: none">• Bone imaging^j: recommended if T2 and PSA >10 ng/mL• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement• <u>If regional or distant metastases are found</u>, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Not routinely recommended	See PROS-7*
High	<ul style="list-style-type: none">• T3a OR• Grade Group 4 or Grade Group 5 OR• PSA >20 ng/mL			<ul style="list-style-type: none">• Bone imaging^j: recommended• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement• <u>If regional or distant metastases are found</u>, see PROS-9	Recommended ^{c,k}	Not routinely recommended	See PROS-8*
Very high	<ul style="list-style-type: none">• T3b-T4 OR• Primary Gleason pattern 5 OR• >4 cores with Grade Group 4 or 5			<ul style="list-style-type: none">• Bone imaging^j: recommended• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement• <u>If regional or distant metastases are found</u>, see PROS-9	Recommended ^{c,k}	Not routinely recommended	See PROS-8*

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PROS-2

homologous DNA repair genes) and Lynch syndrome (resulting from germline mutations in DNA mismatch repair [MMR] genes).^{23–27} In fact, approximately 11% of patients with prostate cancer and at least 1 additional primary cancer carry germline mutations associated with increased cancer risk.²⁸ Therefore, the panel recommends a thorough review of personal and family history for all patients with prostate cancer.

The newfound appreciation of the frequency of germline DNA repair gene mutations (discussed in more detail subsequently) has implications for family genetic counseling, cancer risk syndromes, and assessment of personal risk for second cancers. Some patients with prostate cancer and their families may be at increased risk for breast and ovarian cancer, melanoma, and pancreatic cancer (HBOC), colorectal cancers (Lynch syndrome), and other cancer types. Data also suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have increased risk of progression on local therapy and decreased overall survival (OS).^{29–31} This information should be discussed with such men if they are considering active surveillance. Finally, there are possible treatment implications for patients with DNA repair defects (see

“Treatment Implications for Patients with DNA Repair Gene Mutations,” page 497).

Prostate cancer is often associated with somatic mutations that occur in the tumor but not in the germline. An estimated 89% of metastatic castration-resistant prostate cancer (CRPC) tumors contain a potentially actionable mutation, with only about 9% of these occurring in the germline.³² Both germline and tumor mutations are discussed herein.

Homologous DNA Repair Genes

Somatic mutations in DNA repair pathway genes occur in a reported 19% of localized prostate tumors and 23% of metastatic CRPC tumors, with most mutations found in *BRCA2* and *ATM*.^{32,33} These tumor mutations are often associated with germline mutations. For example, 42% of patients with metastatic CRPC and somatic mutations in *BRCA2* were found to carry the mutation in their germlines.³² In localized prostate cancer, that number was 60%.³³ In fact, recent data indicate that 11.8% of men with metastatic prostate cancer have germline mutations in 1 of 16 DNA repair genes: *BRCA2* (5.3%), *ATM* (1.6%), *CHEK2* (1.9%), *BRCA1* (0.9%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*,

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

FOOTNOTES

- ^c Family history for known germline variants and genetic testing for germline variants should include *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *CHEK2*. Consider cancer predisposition NGS panel testing, which includes *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Additional genes may be appropriate depending on clinical context. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease, but testing may be valuable for family counseling.
- ^f For asymptomatic patients in very-low-, low-, and intermediate-risk groups with life expectancy ≤ 5 years, no further workup or treatment is indicated until the patient becomes symptomatic.
- ^g An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) counts as a single positive core.
- ^h See Principles of Imaging (PROS-B*).
- ⁱ Bone imaging should be performed for any patient with symptoms consistent with bone metastases.
- ^j Plain films, CT, MRI, F-18 sodium fluoride PET/CT or PET/MRI, C-11 choline PET/CT or PET/MRI, or F-18 fluciclovine PET/CT or PET/MRI can be considered for equivocal results on initial bone scan. See PROS-B*.
- ^k The prevalence of inherited (germline) DNA repair gene mutations in men with metastatic prostate cancer, unselected for family history ($n = 692$), was found to be 11.8% (*BRCA2* 5.3%, *ATM* 1.6%, *CHEK2* 1.9%, *BRCA1* 0.9%, *RAD51D* 0.4%, and *PALB2* 0.4%), and 6% in the localized high-risk population in the TCGA cohort (Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. *Cell* 2015;163:1011-25; Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375:443-453). Germline genetic testing is recommended for all men with high-risk, very-high-risk, regional, or metastatic prostate cancer. Genetic counseling resources and support is critical and pre-test counseling is preferred when feasible. Post-test genetic counseling is recommended if a mutation is identified.
- ^l Patients should be informed that somatic tumor sequencing has the potential to uncover germline findings. However, virtually no NGS tests are designed or validated for germline assessment. Therefore, overinterpretation of germline findings should be avoided. If a germline mutation is suspected, the patient should be recommended for genetic counseling and follow-up dedicated germline testing.
- ^m Men with low or favorable intermediate-risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, and ProMark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN or CAPRA risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. See Discussion.

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PROS-3

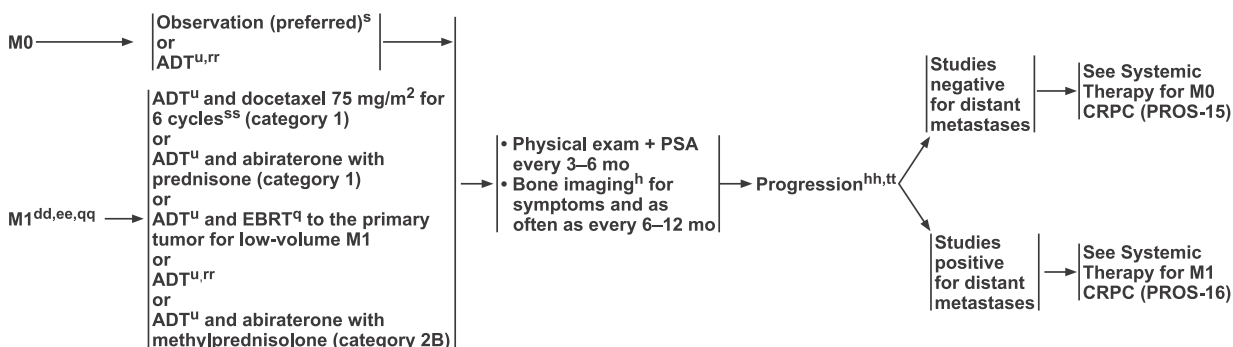
RAD51C, *MRE11A*, *BRIP1*, or *FAM175A*.³⁴ In patients with localized prostate cancer in the TCGA (Cancer Genome Atlas) cohort,³³ the rates of germline DNA repair mutations were 6% in those with high-risk prostate cancer and 2% in low/intermediate risk.³⁴ In another study, 16% of unselected patients with metastatic CRPC harbored germline mutations in *BRCA2*, *ATM*, and *BRCA1*.³⁵

An additional study showed that 9 of 125 men with high-risk, very-high-risk, or metastatic prostate cancer (7.2%) had pathogenic germline mutations in *MUTYH* (4), *ATM* (2), *BRCA1* (1), *BRCA2* (1), and *BRIP1* (1).³⁶ In this study, the rate of mutation identification in men with metastatic disease was 28.6% (2 of 7 men). Although having a relative with breast cancer was associated with germline mutation identification ($P = .035$), only 45.5% of the mutation carriers in the study had mutations that were concordant with their personal and family history. Another study also found that a family history of breast cancer increased the chances of identifying a germline DNA repair gene mutation in men with prostate cancer (odds ratio [OR], 1.89; 95% CI, 1.33–2.68; $P = .003$).³⁷ In a study of an unselected cohort of 3,607 patients with a personal history of prostate cancer who had germline genetic testing based on clinician referral, 11.5% had

germline mutations in *BRCA2*, *CHEK2*, *ATM*, *BRCA1*, or *PALB2*.³⁸

More than 2% of Ashkenazi Jews carry germline mutations in *BRCA1* or *BRCA2*, and these carriers have a 16% chance (95% CI, 4%–30%) of developing prostate cancer by the age of 70.³⁹ In a study of 251 unselected Ashkenazi Jewish patients with prostate cancer, 5.2% had germline mutations in *BRCA1* and *BRCA2*, compared with 1.9% of control Ashkenazi Jewish men.⁴⁰

Germline *BRCA1* or *BRCA2* mutations have been associated with an increased risk for prostate cancer in numerous reports.^{26,27,40–50} In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association of *BRCA1* mutations and increased risks for prostate cancer are less consistent.^{26,27,40,42,44,49} In addition, limited data suggest that germline mutations in *ATM*, *PALB2*, and *CHEK2* increase the risk of prostate cancer.^{51–54} Furthermore, prostate cancer in men with germline *BRCA* mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in noncarrier patients.^{30,31,55–58}

SYSTEMIC THERAPY FOR CASTRATION-NAIVE DISEASE^{jj,pp}^h See Principles of Imaging (PROS-B*).^q See Principles of Radiation Therapy (PROS-D*).^s Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C*).^u See Principles of Androgen Deprivation Therapy (PROS-F*).^{dd} DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI is used, testing using an NGS assay validated for prostate cancer is preferred. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC (see PROS-17 and PROS-18). Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or NGS. J Immunother Cancer 2018;6:29.^{ee} Consider evaluating tumor for alterations in homologous recombination DNA repair such as: *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2*. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, and/or eligibility for clinical trials (eg, PARP inhibitors). Clinical trials may include additional candidate DNA repair genes under investigation as molecular biomarkers. If mutations in *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, or *PALB2* are found and/or there is a strong family history of cancer, refer to genetic counseling to assess for the possibility of HBOC.

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^{hh} Workup for progression should include bone imaging, chest CT, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 sodium fluoride PET/CT or PET/MRI for further soft tissue and bone evaluation or F-18 sodium fluoride PET/CT or PET/MRI for further bone evaluation. The Panel remains unsure what to do when M1 is suggested by modern imaging but not on conventional imaging. See Principles of Imaging (PROS-B*) and Discussion.^{jj} The term "castration-naïve" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naïve" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.^{pp} EBRT to sites of metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.^{qq} ADT alone (see PROS-F*) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.^{rr} Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F*).^{ss} 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.^{tt} Assure castrate level of testosterone.

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PROS-14

DNA MMR Genes

Tumor mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* may result in tumor microsatellite instability (MSI) and defective MMR (dMMR; detected by immunohistochemistry) and are sometimes associated with germline mutations and Lynch syndrome. In a study of >15,000 patients with cancer treated at Memorial Sloan Kettering Cancer Center who had their tumor and matched normal DNA sequenced and tumor MSI status assessed, approximately 5% of 1,048 patients with prostate cancer had MSI-high (MSI-H) or MSI-indeterminate tumors, 5.6% of whom were found to have Lynch syndrome (0.29% of patients with prostate cancer).²³ In another prospective case series, the tumors of 3.1% of 1,033 patients with prostate cancer demonstrated MSI-H/dMMR status, and 21.9% of these patients had Lynch syndrome (0.68% of the total population).⁵⁹ In a study of an unselected cohort of 3,607 patients with a personal history of prostate cancer who had germline genetic testing based on clinician referral, 1.7% had germline mutations in *PMS2*, *MLH1*, *MSH2*, or *MSH6*.³⁸

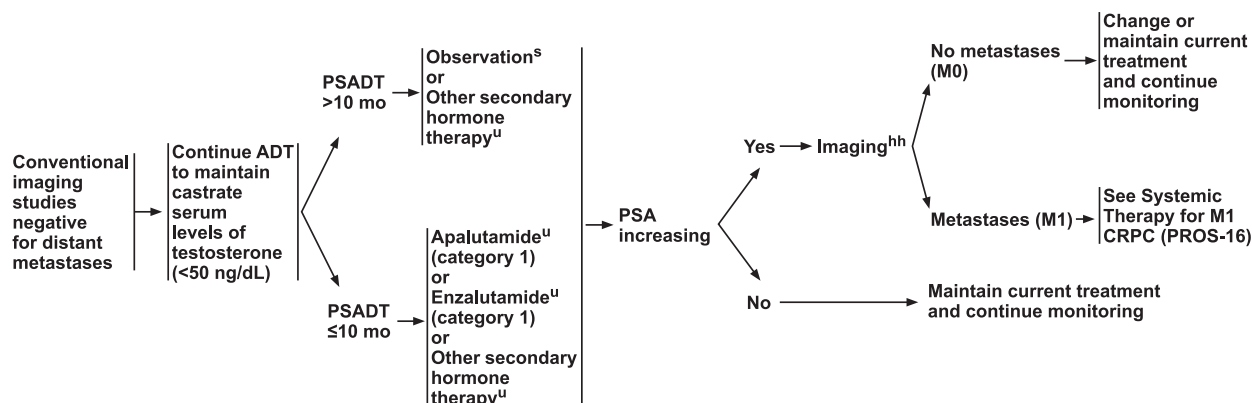
Effect of Intraductal or Ductal Histology

Ductal prostate carcinomas are rare, accounting for approximately 1.3% of prostate carcinomas.⁶⁰ Intraductal

prostate cancer may be more common, especially in higher risk groups.⁶¹ It is important to note that there is significant overlap in diagnostic criteria and that intra-ductal, ductal, and invasive cribriform features may coexist in the same biopsy. By definition, intraductal carcinoma includes cribriform proliferation of malignant cells as long as they remain confined to a pre-existing gland that is surrounded by basal cells. These features are seen frequently with an adjacent invasive cribriform component and would be missed without the use of basal cell markers.

Limited data suggest that prostate tumors with ductal or intraductal histology have increased genomic instability.⁶²⁻⁶⁴ In particular, tumors with these histologies may be more likely to harbor somatic and/or germline MMR gene alterations than those with adenocarcinoma histology.^{65,66} In addition, limited data suggest that germline homologous DNA repair gene mutations may be more common in prostate tumors of ductal or intraductal origin^{67,68} and that intraductal histology is common in germline *BRCA2* mutation carriers with prostate cancer.⁶⁹ Overall, the panel believes that the data connecting histology and the presence of genomic alterations are stronger for intraductal than ductal histology at this time. Therefore, patients with the

SYSTEMIC THERAPY FOR M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)



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^s Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C*).

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

^{hh} Workup for progression should include bone imaging, chest CT, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue and bone evaluation or F-18 sodium fluoride PET/CT or PET/MRI for further bone evaluation. The Panel remains unsure what to do when M1 is suggested by modern imaging but not on conventional imaging. See Principles of Imaging (PROS-B*) and Discussion.

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PROS-15

presence of intraductal carcinoma on biopsy should have germline testing as described subsequently.

Genetic Testing Recommendations

Germline Testing Based on Family History, Histology, and Risk Groups

The panel recommends inquiring about family and personal history of cancer at time of initial diagnosis. Based on the data discussed previously, the panel recommends *germline* genetic testing, with or without pretest genetic counseling, for patients with prostate cancer and any of the following:

- A positive family history (see definition in the guidelines)
- High-risk, very-high-risk, regional, or metastatic prostate cancer, regardless of family history
- Ashkenazi Jewish ancestry
- Intraductal histology

Germline testing, when performed, should include *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome) and the homologous recombination genes *BRCA2*, *BRCA1*, *ATM*, *PALB2*, and *CHEK2*. A cancer predisposition next-generation sequencing (NGS) panel testing, at a minimum including *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*,

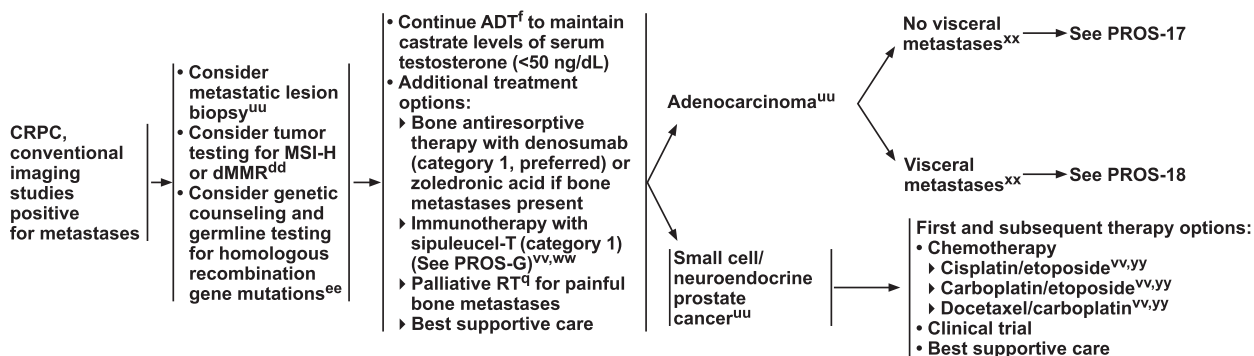
and *PMS2*, can be considered. Additional genes may be appropriate depending on clinical context. For example, *HOXB13* is a prostate cancer risk gene and, although there are not currently clear therapeutic implications in the advanced disease setting, testing may be valuable for family counseling.^{70,71}

Somatic Tumor Testing Based on Risk Groups

Tumor testing recommendations are as follows:

1. Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2*) can be considered in patients with regional or metastatic prostate cancer.
2. Tumor testing for MSI or dMMR can be considered in patients with regional or metastatic prostate cancer.
3. Multigene molecular testing can be considered for patients with low- and favorable-intermediate risk prostate cancer and life expectancy ≥ 10 years (see "Tumor Multigene Molecular Testing," page 488).
4. The Decipher molecular assay can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B; see "Tumor Multigene Molecular Testing," page 488).

SYSTEMIC THERAPY FOR M1 CRPC



*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

^f See Principles of Androgen Deprivation Therapy (PROS-F*).

^q See Principles of Radiation Therapy (PROS-D*).

^{dd} DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI is used, testing using an NGS assay validated for prostate cancer is preferred. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC (see PROS-17 and PROS-18). Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or NGS. *J Immunother Cancer* 2018;6:29.

^{ee} Consider evaluating tumor for alterations in homologous recombination DNA repair such as: *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2*. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, and/or eligibility for clinical trials (eg, PARP inhibitors). Clinical trials may include additional candidate DNA repair genes under investigation as molecular biomarkers. If mutations in *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, or *PALB2* are found and/or there is a strong family history of cancer, refer to genetic counseling to assess for the possibility of HBOC.

^{uu} Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed.

^{vv} See Principles of Immunotherapy and Chemotherapy (PROS-G*).

^{ww} Sipuleucel-T has not been studied in patients with visceral metastases.

Sipuleucel-T is not recommended for patients with small cell/neuroendocrine prostate cancer.

^{xx} Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases. ^{yy} See NCCN Guidelines for Small Cell Lung Cancer[†].

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PROS-16

If mutations in *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, or *PALB2* are found, the patient should be referred for genetic counseling to assess for the possibility of HBOC.

If MSI testing is performed, testing using an NGS assay validated for prostate cancer is preferred.⁷²⁻⁷⁴ If MSI-H or dMMR is found, the patient should be referred for genetic counseling to assess for the possibility of Lynch syndrome. MSI-H or dMMR indicate eligibility for pembrolizumab in second and subsequent lines of treatment of CRPC (see “Pembrolizumab,” page 496).

Patients should be informed that somatic tumor sequencing has the potential to uncover germline findings. However, virtually none of the NGS tests are designed or validated for germline assessment. Therefore, overinterpretation of germline findings should be avoided. If a germline mutation is suspected, the patient should be recommended for genetic counseling and follow-up dedicated germline testing.

Additional Testing

Tumors from most patients with metastatic CRPC harbor mutations in genes involved in the androgen receptor

signaling pathway.³² AR-V7 testing in circulating tumor cells can be considered to help guide selection of therapy in the postabiraterone/enzalutamide metastatic CRPC setting (discussed in more detail in “Progression After Enzalutamide or Abiraterone,” available online, in these guidelines, at NCCN.org).

Risk Stratification For Clinically Localized Disease

Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is adjuvant or salvage radiation to control cancer after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by a digital rectal exam and radiographically determined clinical T stage, Gleason score and extent of cancer in the biopsy specimen, and serum PSA level. Imaging studies (ie, ultrasound, MRI) have been investigated intensively but have yet to be accepted as essential adjuncts to staging.

The NCCN Guidelines have, for many years, incorporated a risk stratification scheme that uses a minimum

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA WITHOUT VISCERAL METASTASES^{xx,bbb}
FIRST-LINE TREATMENT

- Abiraterone^u with prednisone (category 1)
- Docetaxel^{vv,zz} (category 1)
- Enzalutamide^u (category 1)
- Radium-223^{aaa} for symptomatic bone metastases (category 1)
- Abiraterone^u with methylprednisolone
- Clinical trial
- Other secondary hormone therapy^u

Prior therapy
abiraterone/
enzalutamide
ccc,ddd,eee

Prior therapy
docetaxel
ddd,eee

SECOND-LINE TREATMENT

- Docetaxel^{vv} (category 1)
- Radium-223^{aaa} for symptomatic bone metastases (category 1)
- Pembrolizumab for MSI-H or dMMR (category 2B)
- If not previously received:
 - ▶ Abiraterone^u with prednisone
 - ▶ Abiraterone^u with methylprednisolone
 - ▶ Enzalutamide^u
 - ▶ Sipuleucel-T^{vv,ww}
 - ▶ Clinical trial
 - ▶ Other secondary hormone therapy^u
 - ▶ Best supportive care
- Abiraterone^u with prednisone (category 1)
- Cabazitaxel (category 1)^{vv}
- Enzalutamide (category 1)^u
- Radium-223^{aaa} for symptomatic bone metastases (category 1)
- Abiraterone^u with methylprednisolone
- Pembrolizumab for MSI-H or dMMR (category 2B)
- If not previously received:
 - ▶ Sipuleucel-T^{vv,ww}
 - ▶ Clinical trial
 - ▶ Consider docetaxel rechallenge^{vv,fff}
 - ▶ Mitoxantrone with prednisone^{vv,ggg}
 - ▶ Other secondary hormone therapy^u
 - ▶ Best supportive care

SUBSEQUENT TREATMENT

- At progression^{ddd,eee}:
- If not previously received:
 - ▶ Abiraterone^u with prednisone (category 1)
 - ▶ Enzalutamide^u (category 1)
 - ▶ Cabazitaxel^{vv} (category 1)
 - ▶ Radium-223^{aaa} for symptomatic bone metastases (category 1)
 - ▶ Abiraterone^u with methylprednisolone
 - ▶ Mitoxantrone with prednisone^{vv,ggg}
 - ▶ Pembrolizumab for MSI-H or dMMR (category 2B)
 - Clinical trial
 - Docetaxel rechallenge^{vv,fff}
 - Other secondary hormone therapy^u
 - Best supportive care

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

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

^{vv} See Principles of Immunotherapy and Chemotherapy (PROS-G*).

^{ww} Sipuleucel-T has not been studied in patients with visceral metastases.

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

^{zz} 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.

^{aaa} Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D*).

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

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

^{ddd} Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. See Principles of Imaging (PROS-B*) and Discussion.

^{eee} If visceral mets are found, see PROS-18. If small cell neuroendocrine is found, see PROS-16.

^{fff} Patients who received docetaxel with ADT in the metastatic castration-naïve setting can be considered for docetaxel rechallenge in the CRPC setting.

^{ggg} Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies.

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PROS-17

of stage, Gleason grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical recurrence after definitive local therapy.⁷⁵ Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.^{76,77}

A new prostate cancer grading system was developed during the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.⁷⁸ Several changes were made to the assignment of Gleason pattern based on pathology. The new system assigns Grade Groups from 1 to 5, derived from the Gleason score.

- Grade Group 1: Gleason score ≤ 6 ; only individual discrete well-formed glands
- Grade Group 2: Gleason score $3+4=7$; predominantly well-formed glands with lesser component of poorly formed/fused/cirriiform glands
- Grade Group 3: Gleason score $4+3=7$; predominantly poorly formed/fused/cirriiform glands with lesser component of well-formed glands
 - For cases with $>95\%$ poorly formed/fused/cirriiform glands or lack of glands on a core or at radical

prostatectomy, the component of $<5\%$ well-formed glands is not factored into the grade.

- Grade Group 4: Gleason score $4+4=8$; $3+5=8$; $5+3=8$
 - Only poorly formed/fused/cirriiform glands or
 - Predominantly well-formed glands and lesser component lacking glands (poorly formed/fused/cirriiform glands can be a more minor component) or
 - Predominantly lacking glands and lesser component of well-formed glands (poorly formed/fused/cirriiform glands can be a more minor component)
- Grade Group 5: Gleason score 9–10; lack gland formation (or with necrosis) with or without poorly formed/fused/cirriiform glands
 - For cases with $>95\%$ poorly formed/fused/cirriiform glands or lack of glands on a core or at radical prostatectomy, the component of $<5\%$ well-formed glands is not factored into the grade.

Many experts believe that ISUP Grade Groups will enable patients to better understand their true risk level and thereby limit overtreatment. The new Grade Group system was validated in 2 separate cohorts, one of $>26,000$ men and one of 5,880 men, treated for prostate

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA WITH VISCERAL METASTASES ^{xx,bbb}

FIRST-LINE TREATMENT

- Docetaxel^{vv} (category 1)
- Enzalutamide^u (category 1)
- Abiraterone^u with prednisone
- Abiraterone^u with methylprednisolone
- Clinical trial
- Mitoxantrone with prednisone^{vv,ggg}
- Other secondary hormone therapy^u

Prior therapy
enzalutamide/
abiraterone^{ccc,ddd,hhh}

Prior therapy
docetaxel^{ddd,hhh}

SECOND-LINE TREATMENT

- Docetaxel^{vv} (category 1)
- If not previously received:
 - ▶ Abiraterone^u with prednisone
 - ▶ Abiraterone^u with methylprednisolone
 - ▶ Enzalutamide^u
 - ▶ Cabazitaxel^{vv}
- Pembrolizumab for MSI-H or dMMR (category 2B)
- Clinical trial
- Other secondary hormone therapy^u
- Best supportive care

- Abiraterone^u with prednisone (category 1)
- Enzalutamide^u (category 1)
- Cabazitaxel^{vv} (category 1)
- Abiraterone^u with methylprednisolone
- Pembrolizumab for MSI-H or dMMR (category 2B)
- Clinical trial
- Docetaxel rechallenge^{vv,fff}
- Mitoxantrone with prednisone^{vv,ggg}
- Other secondary hormone therapy^u
- Best supportive care

SUBSEQUENT TREATMENT
(category 2B)

- At progression^{dd,hhh}:
- If not previously received:
 - ▶ Enzalutamide^u
 - ▶ Cabazitaxel^{vv}
 - ▶ Abiraterone^u with prednisone
 - ▶ Abiraterone^u with methylprednisolone
- Mitoxantrone with prednisone^{vv,ggg}
- Pembrolizumab for MSI-H or dMMR
- Clinical trial
- Docetaxel rechallenge^{vv,fff}
- Other secondary hormone therapy^u
- Best supportive care

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

^{vv} See Principles of Immunotherapy and Chemotherapy (PROS-G*).

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

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

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

^{ddd} Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. See Principles of Imaging (PROS-B*) and Discussion.

^{fff} Patients who received docetaxel with ADT in the metastatic castration-naïve setting can be considered for docetaxel rechallenge in the CRPC setting.

^{ggg} Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies.

^{hhh} Patients treated with systemic therapy for non-visceral metastases (see PROS-17) should proceed to a different subsequent therapy for patients with visceral metastases based on their previous treatment. If small cell neuroendocrine is found, see PROS-16.

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PROS-18

cancer with either radical prostatectomy or radiation.^{79,80} Both studies found that Grade Groups predicted the risk of recurrence after primary treatment. For instance, in the larger study, the 5-year biochemical recurrence-free progression probabilities after radical prostatectomy for Grade Groups 1 through 5 were 96% (95% CI, 95–96), 88% (95% CI, 85–89), 63% (95% CI, 61–65), 48% (95% CI, 44–52), and 26% (95% CI, 23–30), respectively. The separation between Grade Groups was less pronounced in the radiation therapy (RT) cohort, likely because of increased use of neoadjuvant/concurrent/adjuvant androgen deprivation therapy (ADT) in the higher risk groups. In another study of the new ISUP Grade Group system, all-cause mortality and prostate cancer-specific mortality were higher in men in Grade Group 5 than in those in Grade Group 4.⁸¹ Additional studies have supported the validity of this new system.^{82–86} The NCCN Panel has accepted the new Grade Group system to inform better treatment discussions compared with those using Gleason score. Patients remain divided into very low-, low-, intermediate-, high-, and very high-risk groups.

The NCCN Guidelines Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed that men assigned to

the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than men categorized according to Gleason score (7) or PSA level (10–20 ng/mL).⁸⁷ A similar trend of superior recurrence-free survival was observed in men placed in the high-risk group by clinical stage (T3a) compared with those assigned by Gleason score (8–10) or PSA level (>20 ng/mL), although it did not reach statistical significance. Other studies have reported differences in outcomes in the high-risk group depending on risk factors or primary Gleason pattern.^{88,89} Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.^{90,91}

In a retrospective study, 1,024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.⁹² Multivariate analysis revealed that primary Gleason pattern 4, number of positive biopsy cores ≥50%, and presence of >1 intermediate-risk factors (ie, T2b–c, PSA 10–20 ng/mL, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors used these factors to separate the patients into unfavorable and favorable intermediate-risk groups and determined that the unfavorable intermediate-risk group had worse PSA

recurrence-free survival and higher rates of distant metastasis and prostate cancer-specific mortality than the favorable intermediate-risk group. The use of active surveillance in men with favorable intermediate risk prostate cancer is discussed subsequently (see “Favorable Intermediate Risk,” available online, in these guidelines, at NCCN.org).

Nomograms

The more clinically relevant information that is used in the calculation of time to PSA recurrence, the more accurate the result. A nomogram is a predictive instrument that takes a set of input data (variables) and makes predictions about an outcome. Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables. The Partin tables were the first to achieve widespread use for counseling men with clinically localized prostate cancer.^{93–96} The tables give the probability (95% CI) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage. Nomograms can be used to inform treatment decision-making for men contemplating active surveillance,^{97–99} radical prostatectomy,^{100–103} neurovascular bundle preservation,^{104–106} or omission of pelvic lymph node dissection during radical prostatectomy,^{107–110} brachytherapy,^{100,111–113} or external beam RT (EBRT).^{100,114} Biochemical progression-free survival (PFS) can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.^{100,115–117} Potential success of adjuvant or salvage RT after unsuccessful radical prostatectomy can be assessed using a nomogram.^{100,118}

None of the current models predicts with perfect accuracy, and only some of these models predict metastasis^{99,100,115,119,120} and cancer-specific death.^{101,103,121–123} Given the competing causes of mortality, many men who sustain PSA recurrence will not live long enough to develop clinical evidence of distant metastases or to die of prostate cancer. Those with a short PSA doubling time (PSADT) are at greatest risk of death. Not all PSA recurrences are clinically relevant; thus, PSADT may be a more useful measure of risk of death.¹²⁴ The NCCN Guidelines Panel recommends that NCCN risk groups be used to begin the discussion of options for the treatment of clinically localized prostate cancer and that nomograms be used to provide additional and more individualized information.

Tumor Multigene Molecular Testing

Personalized or precision medicine is a goal for many translational and clinical investigators. The National Academy of Medicine has described several lessons that should accelerate the development of useful biomarkers¹²⁵ to inform men and their physicians about

proper choices for treatment of clinically localized prostate cancer. Dr. Hayes has warned that a “bad tumor marker is as bad as a bad drug.”^{126,127} The NCCN Prostate Cancer Guidelines Panel strongly advocates for use of life expectancy estimation, use of nomograms, and active surveillance as the *only* option for men with low-risk prostate cancer and life expectancy less than 10 years or very low-risk prostate cancer and life expectancy less than 20 years. Although risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about the risk of disease progression persists. American men continue to under-select active surveillance and their physicians may under-recommend it, likely as a result of this uncertainty.¹²⁸ In 2013, <20% of men with low-risk prostate cancer were managed using active surveillance.¹⁶ However, active surveillance has become more common in some areas, such as Michigan, where its frequency has been measured and educational efforts have begun.^{129,130}

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment of recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation or salvage EBRT.^{131–140} A prospective, clinical utility study of 3,966 patients newly diagnosed with localized prostate cancer found that the rates of active surveillance increased with use of a tissue-based gene expression classifier.¹⁴¹ Active surveillance rates were 46.2%, 75.9%, and 57.9% for those whose classifier results were above the specified threshold, below the threshold, and those who did not undergo genomic testing, respectively ($P < .001$). The authors estimate that 1 additional patient may choose active surveillance for every 9 men with favorable risk prostate cancer who undergo genomic testing.

No randomized controlled trials have studied the utility of these tests. Several of these assays are available, and 4 have received positive reviews by the Molecular Diagnostic Services Program (MolDX) and are likely to be covered by CMS (Centers for Medicare & Medicaid Services). Several other tests are under development, and the use of these assays is likely to increase in the coming years.

Table 1 lists these tests in alphabetical order and provides an overview of each test, populations in which each test independently predicts outcome, and supporting references. These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. The panel believes that men with low or favorable intermediate disease may consider the use of Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification. In addition, Decipher may be considered during workup for radical prostatectomy PSA persistence or recurrence (category 2B). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

Androgen Deprivation Therapy

ADT is administered as primary systemic therapy for regional or advanced disease and as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers.

In the community, ADT has been commonly used as primary therapy for early-stage, low-risk disease, especially in the elderly. This practice has been challenged by a large cohort study of 66,717 elderly men with T1–T2 tumors.¹⁴² No 15-year survival benefit was found in patients receiving ADT compared with observation alone. Similarly, another cohort study of 15,170 men diagnosed with clinically localized prostate cancer who were not treated with curative intent therapy reported no survival benefit from primary ADT after adjusting for demographic and clinical variables.¹⁴³ Placing patients with early prostate cancer on ADT should not be routine practice.

Antiandrogen monotherapy (bicalutamide) after completion of primary treatment was investigated as an adjuvant therapy in patients with localized or locally advanced prostate cancer, but results did not support its use in this setting.^{144,145}

Castrate levels of serum testosterone (<50 ng/dL; <1.7 nmol/L) should be achieved with ADT, because low nadir serum testosterone levels were shown to be associated with improved cause-specific survival in the PR-7 study.¹⁴⁶

ADT for Castration-Naïve Disease

The term “castration-naïve” is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term “castration-naïve” even when patients have had neoadjuvant, concurrent, and/or adjuvant ADT as part of RT provided they have recovered testicular function.

ADT for castration-naïve prostate cancer can be accomplished using bilateral orchiectomy, a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or an LHRH agonist plus a first-generation antiandrogen. As discussed subsequently, abiraterone or docetaxel can be added to orchiectomy, LHRH agonist, or LHRH antagonist for M1 disease. For patients with M0 disease, observation is preferred over ADT.

LHRH agonists and LHRH antagonists appear equally effective in patients with advanced prostate cancer.¹⁴⁷ Medical or surgical castration combined with an antiandrogen is known as combined androgen blockade. No prospective randomized studies have demonstrated a survival advantage with combined androgen blockade over the serial use of an LHRH agonist and an antiandrogen.¹⁴⁸ Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in OS by 5%–20% over LHRH agonist monotherapy.^{149,150} However, others have concluded that more complete disruption of the androgen axis (with finasteride, dutasteride, or antiandrogen added to medical or surgical castration) provides little if any benefit over castration alone.¹⁵¹

Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended for primary ADT. Furthermore, dutasteride plus bicalutamide showed no benefit over bicalutamide alone in patients with locally advanced or metastatic prostate cancer.¹⁵²

Recent evidence suggests that orchiectomy may be safer than an LHRH agonist. Four hundred twenty-nine men with metastatic prostate cancer who underwent orchiectomy were compared with 2,866 men who received LHRH agonist between 1995 and 2009. Orchiectomy was associated with lower risk of fracture, peripheral arterial disease, and cardiac-related complications, although risk was similar for diabetes, deep vein thrombosis, pulmonary embolism, and cognitive disorders.¹⁵³ Posthoc analysis of a randomized trial of LHRH antagonist versus LHRH agonist found lower risk of cardiac events in patients with existing cardiac disease treated with LHRH antagonist.¹⁵⁴ The heart and T lymphocytes have receptors for LHRH. Therefore, LHRH agonists may affect cardiac contractility, vascular plaque stability, and inflammation.¹⁵⁵

ADT for M0 Biochemical Recurrence

Controversy remains about the timing and duration of ADT when local therapy has failed. Many believe that early ADT is best, but cancer control must be balanced against side effects. Early ADT is associated with increased side effects and the potential development of the metabolic syndrome.

Patients with an increasing PSA level and with no symptomatic or clinical evidence of cancer after

Table 1. Available Tissue-Based Tests for Prostate Cancer Risk Stratification/Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post RP, adverse pathology/high-risk features Post RP, biochemical recurrence Post RP, adjuvant, or salvage radiation Biopsy, localized prostate cancer post RP or EBRT	<ul style="list-style-type: none"> • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • Gleason grade ≥ 4 disease at RP • Adverse pathologic features at RP 	136,139,140,234–249	Cover postbiopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT Biopsy, conservatively managed (active surveillance)	<ul style="list-style-type: none"> • Metastasis • Prostate cancer-specific mortality 	250–253	Not recommended
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	<ul style="list-style-type: none"> • Non-organ-confined pT3 or Gleason grade 4 disease on RP 	135,254–257	Cover postbiopsy for NCCN very low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	TURP, conservatively managed (active surveillance) Biopsy, conservatively managed (active surveillance) Biopsy, localized prostate cancer Biopsy, intermediate-risk treated with EBRT RP, node-negative localized prostate cancer	<ul style="list-style-type: none"> • Prostate cancer-specific mortality • Prostate cancer-specific mortality • Biochemical recurrence • Metastasis • Biochemical recurrence • Biochemical recurrence 	131–134,258–260	Cover postbiopsy for NCCN very low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	<ul style="list-style-type: none"> • Non-organ-confined pT3 or Gleason pattern 4 disease on RP 	261	Cover postbiopsy for NCCN very low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy.
PTEN	Fluorescent in situ hybridization or IHC	TURP, conservatively managed (active surveillance) Biopsy, Gleason grade 3+3 RP, high-risk localized disease	<ul style="list-style-type: none"> • Prostate cancer-specific mortality • Upgrading to Gleason pattern 4 on RP • Biochemical recurrence 	262–266	Not recommended

Abbreviations: EBRT, external beam radiation therapy; FFPE, formalin-fixed, paraffin-embedded; IHC, immunohistochemistry; PORTOS, postoperative radiation sensitivity; PSA, prostate-specific antigen; RP, radical prostatectomy; TURP, transurethral resection of prostate.

definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. Timing of ADT for patients whose only evidence of cancer is increasing PSA is influenced by PSA velocity (PSADT), patient and physician anxiety, the short-term and long-term side effects of ADT, and underlying comorbidities of the patient. Early ADT is acceptable, but an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (ie, what level of PSA) remain controversial. The multicenter phase 3 TROG 03.06/VCOG PR 01-03 [TOAD] trial randomized 293 men with PSA relapse after operation or radiation (n=261) or who were not considered for curative treatment (n=32) to immediate ADT or ADT delayed by a recommended interval of ≥ 2 years.¹⁵⁶ Five-year OS was improved in the immediate therapy arm compared with the delayed therapy arm (91.2% vs 86.4%; log-rank $P=.047$). No significant differences were seen in the secondary endpoint of global health-related QOL at 2 years.¹⁵⁷ In addition, there were no differences over 5 years in global QOL, physical functioning, role or emotional functioning, insomnia, fatigue, dyspnea, or feeling less masculine. However, sexual activity was lower and the hormone-treatment-related symptoms score was higher in the immediate ADT group compared with the delayed ADT group. Most clinical trials in this patient population require PSA level ≥ 0.5 mg/dL (after radical prostatectomy) or “nadir + 2” (after radiation) for enrollment.

The panel believes that the benefit of early ADT is uncertain and must be balanced against the risk of ADT side effects. Patients with an elevated PSA and/or a shorter PSADT (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

Primary ADT for M1 Castration-Naïve Prostate Cancer

ADT is the gold standard for initial treatment of patients with metastatic disease at presentation.¹⁴⁸ A PSA value ≤ 4 ng/mL after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.¹⁵⁸

ADT options for M1 castration-naïve disease are:

- Orchiectomy \pm docetaxel
- LHRH agonist alone \pm docetaxel
- LHRH agonist plus first-generation antiandrogen \pm docetaxel
- LHRH antagonist \pm docetaxel
- Orchiectomy plus abiraterone
- LHRH agonist plus abiraterone
- LHRH antagonist plus abiraterone

In patients with overt metastases in weight-bearing bone who are at risk for developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, antiandrogen therapy should precede or be coadministered with LHRH agonist for at least 7 days to diminish ligand binding to the androgen receptor.^{159,160} LHRH antagonists rapidly and directly inhibit the release of androgens, unlike LHRH agonists that initially stimulate LHRH receptors before hypogonadism. Therefore, no initial flare is associated with these agents and coadministration of antiandrogen is unnecessary.

The data supporting the addition of abiraterone or docetaxel to ADT in this setting are discussed subsequently. ADT with addition of EBRT to the primary tumor for low volume metastatic disease is discussed in “EBRT to the Primary Tumor in Low Volume M1 Disease” (available online, in these guidelines, at NCCN.org).

Abiraterone Acetate in Castration-Naïve Prostate Cancer

In February 2018, the FDA approved abiraterone in combination with prednisone for metastatic castration-naïve prostate cancer.¹⁶¹ This approval was based on 2 randomized phase 3 clinical trials of abiraterone and low-dose prednisone plus ADT that were reported in men with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease (STAMPEDE and LATITUDE) that demonstrated improved OS over ADT alone.¹⁶² In LATITUDE, 1,199 men with high-risk, metastatic, castration-naïve prostate cancer were randomized to abiraterone with prednisone 5 mg once daily or matching placebos. High-risk disease was defined as at least 2 of the following: Gleason score 8–10, ≥ 3 bone metastases, and visceral metastases.¹⁶² Efficacy was demonstrated at the first interim analysis, and the trial was unblinded. The primary endpoint of OS was met and favored abiraterone (hazard ratio [HR], 0.62; 95% CI, 0.51–0.76; $P<.0001$). Estimated 3-year OS rates improved from 49% to 66% at 30 months follow-up. Secondary endpoints were improved and included delayed castration-resistant radiographic progression (from median 14.8–33.2 months), PSA progression (7.4–33.2 months), time to pain progression, and initiation of chemotherapy.

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.¹⁶² 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 QOL.¹⁶³ A limitation of this trial is that only 27% of placebo-treated men received abiraterone or enzalutamide at progression, and only 52% of these men received any life-prolonging therapy.¹⁶²

A second randomized trial (STAMPEDE) of 1,917 men with castration-naïve prostate cancer showed similar OS benefits.¹⁶⁴ However, unlike LATITUDE, STAMPEDE eligibility permitted men with high-risk N0 M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >40, or Gleason score 8–10; n=509), or N1 M0 disease (pelvic nodal metastases; n=369) in addition to patients with M1 disease, who made up the majority of patients (n=941). The majority of men were newly diagnosed, while a minority of men had recurrent, high-risk, or metastatic disease after local therapy (n=98). Thus, STAMPEDE was a heterogeneous mix of patients with high-risk, nonmetastatic, node-positive, or M1 disease. In M1 patients, 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 men <70 years of age than in older men (HR, 0.94 vs 0.51). Older men also experienced 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 men 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 men compared with deferring therapy to the CRPC setting.

Adverse events in STAMPEDE were similar to that reported in LATITUDE, but were increased in older men, 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 men 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 panel to recommend abiraterone with 5-mg once-daily prednisone as a treatment option with ADT for men with newly diagnosed, M1, castration-naïve prostate cancer (category 1). Alternatively, the fine particle formulation of abiraterone can be used (category 2B; see “Abiraterone Acetate in M1 CRPC,”

page 493). For men undergoing curative-intent treatment of N1 disease, abiraterone can be added to EBRT with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT or can be given with ADT for castration-naïve disease (without EBRT). The fine particle formulation of abiraterone is an option (category 2B; see “Abiraterone Acetate in M1 CRPC”). However, there was insufficient survival, FFS data, and follow-up available to recommend abiraterone for men with high-risk or very high-risk N0 M0 prostate cancer. Further follow-up and dedicated ongoing clinical trials are needed in this curative-intent RT population.

Abiraterone with prednisone can be given at 250 mg/day and administered following a low-fat breakfast, as an alternative to the dose of 1,000 mg/day after an overnight fast (see “Abiraterone Acetate in M1 CRPC,” page 493).¹⁶⁵ The cost saving may reduce financial toxicity and improve compliance.

Secondary Hormone Therapy for CRPC

Most men with advanced disease eventually stop responding to traditional ADT and are categorized as castration-resistant (also known as “castration-recurrent”). Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of men receiving ADT.^{166,167} Androgen signaling consequent to nongonadal sources of androgen in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the metastatic CRPC setting dramatically changed the paradigm of CRPC treatment.

For men who develop CRPC, ADT with an LHRH agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL). Options for secondary hormone therapy include a first-generation antiandrogen, antiandrogen withdrawal, ketoconazole (adrenal enzyme inhibitor) with or without hydrocortisone, corticosteroid, diethylstilbestrol (DES), or other estrogen.^{168,169} However, none of these strategies has yet been shown to prolong survival in randomized clinical trials. New secondary hormone options include abiraterone (M1 only), enzalutamide (M0 or M1), and apalutamide (M0 only), as discussed subsequently.

DES can produce safe chemical castration in many men. Gynecomastia and cardiovascular side effects occur with increasing frequency with increasing dose. Side effects are rare, and survival appears equivalent to that of other means of ADT at a 1-mg daily dose. The mechanism of action of DES remains uncertain because a 1-mg dose does not render some men castrate, and DES produces responses when used in CRPC.¹⁷⁰

Transdermal estradiol may provide similar cancer control with fewer side effects.¹⁷¹ The ongoing PATCH

clinical trial demonstrated similar rates of castrate levels of testosterone, PSA response, and side effects in 85 men treated with LHRH agonist and 168 men treated with 100 mcg/24-hour estrogen patches twice weekly.¹⁷² QOL outcomes and the experience of vasomotor symptoms were better at 6 months in the transdermal group compared with the agonist group, but rates of significant gynecomastia were higher in the transdermal group (37% vs 5%).¹⁷³ The PATCH trial continues enrollment to assess survival (ClinicalTrials.gov identifier: NCT00303784).

Abiraterone Acetate in M1 CRPC

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

FDA approval in the postdocetaxel setting was based on the results of a phase 3, randomized, placebo-controlled trial (COU-AA-301) in men with metastatic CRPC previously treated with docetaxel-containing regimens.^{174,175} 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 vs 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86; $P<.0001$).¹⁷⁵ Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.^{175,176}

FDA approval in the predocetaxel setting occurred on December 10, 2012, and was based on the randomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n=546) versus prednisone alone (n=542) in men with asymptomatic or minimally symptomatic metastatic CRPC.¹⁷⁷ Most men in this trial were not taking narcotics for cancer pain, and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary endpoint of radiographic PFS was improved by treatment from 8.3 to 16.5 months (HR, 0.53; $P<.001$). OS was improved at final analysis with a median follow-up of 49.2 months (34.7 vs 30.3 months; HR, 0.81; 95% CI, 0.70–0.93; $P=.003$).¹⁷⁸ Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment, and PSA declines (62% vs 24% with >50% decline) and radiographic responses (36% vs 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract

infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%).

In May of 2018, the FDA approved a novel, fine-particle formulation of abiraterone, in combination with methylprednisolone, for the treatment of patients with metastatic CRPC.¹⁷⁹ In studies of healthy men, this formulation at 500 mg was shown to be bioequivalent to 1,000 mg of the originator formulation.^{180,181} In a phase 2 therapeutic equivalence study, 53 men with metastatic CRPC who were not treated previously with abiraterone, enzalutamide, radium-223, or chemotherapy (docetaxel for metastatic CRPC completed ≥ 1 year prior to enrollment was allowed) were randomized to 500 mg daily of the new formulation plus 4 mg methylprednisolone orally twice daily or to 1,000 mg of the originator formulation daily plus 5 mg prednisone orally twice daily.¹⁸² 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 men with metastatic CRPC (category 2A), but switching from one formulation to the other on disease progression should not be undertaken. Abiraterone with either steroid should not be given following progression on abiraterone with the other steroid.

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, at least initially, is warranted during abiraterone therapy. Some patients may be able to avoid steroids with abiraterone, but careful monitoring is warranted, and a mineralocorticoid receptor antagonist or steroid should be added to control side effects if necessary.^{183–185} Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

A randomized phase 2 noninferiority study of 75 patients with M1 CRPC compared 1,000 mg/day abiraterone with prednisone after an overnight fast with

250 mg/day after a low-fat breakfast.¹⁶⁵ The primary endpoint was log change in PSA, with secondary endpoints of PSA response ($\geq 50\%$) 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 with prednisone 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. The cost saving may reduce financial toxicity and improve compliance. Food impacts absorption unpredictably; side effects should be monitored and standard dosing (1,000 mg on empty stomach) used if excess toxicity is observed on modified dosing (250 mg with food).

Enzalutamide in M0 and M1 CRPC

On August 31, 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of men with metastatic CRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase 3, placebo-controlled trial (AFFIRM).^{186,187} AFFIRM randomized 1,199 men to enzalutamide or placebo in a 2:1 ratio, and the primary endpoint was OS. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63; $P < .001$). Survival was improved in all subgroups analyzed. Secondary endpoints also were improved significantly, which included the proportion of men 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 flashes (20% vs 10%), headache (12% vs 6%), and seizures (0.6% vs 0%). The incidence of cardiac disorders did not differ between the arms. Enzalutamide is dosed at 160 mg daily. Patients in the AFFIRM study were maintained on GnRH 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.^{186,188}

Another phase 3 trial studied enzalutamide in the prechemotherapy setting. The PREVAIL study randomly assigned 1,717 patients with chemotherapy-naïve metastatic prostate cancer to daily enzalutamide or placebo.^{189,190} 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 also were

observed (eg, the time until chemotherapy initiation or first SRE).

Two randomized clinical trials have reported that enzalutamide may be superior to bicalutamide for cancer control in metastatic CRPC. The TERRAIN study randomized 375 men with treatment-naïve, metastatic CRPC to 160 mg/day enzalutamide or 50 mg/day bicalutamide in a 1:1 manner.¹⁹¹ The enzalutamide group had significantly better PFS (defined as PSA progression, soft tissue progression, or development of additional bony metastases) compared with the bicalutamide group (median time to progression, 15.7 vs 5.8 months; HR, 0.44; 95% CI, 0.34–0.57).

The STRIVE trial randomized 396 men with M0 or M1 treatment-naïve CRPC to 160 mg/d enzalutamide or 50 mg/d bicalutamide in a 1:1 manner.¹⁹² The primary endpoint in this study was PFS, defined as either PSA progression, radiographic progression of disease, or death from any cause. Enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (HR, 0.24; 95% CI, 0.18–0.32). These studies demonstrated that enzalutamide extended PFS better than bicalutamide in men choosing an antiandrogen for secondary hormonal therapy treatment of CRPC. Bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.

Thus, enzalutamide represents a treatment option for men in both the predocetaxel and postdocetaxel metastatic CRPC setting and is a reasonable choice for men who are not candidates for chemotherapy. Patients receiving enzalutamide have no restrictions for food intake, and concurrent prednisone is permitted but not required.¹⁸⁶

The randomized, double-blind, placebo-controlled phase 3 PROSPER trial assessed the use of enzalutamide in 1,401 men with nonmetastatic CRPC.¹⁹³ Men 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 to 0.35; $P < .0001$). No significant difference was seen in OS, although OS data were not mature at the time of final analysis for metastasis-free survival. 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.¹⁹⁴ The FDA expanded approval for enzalutamide to include men with nonmetastatic CRPC on

July 13, 2018,¹⁸⁸ and the panel believes that patients with M0 CRPC can be offered enzalutamide if PSADT is ≤ 10 months (category 1).

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with nonmetastatic CRPC on February 14, 2018.¹⁹⁵ This approval was based on the phase 3 SPARTAN trial of 1,207 patients with M0 CRPC and PSADT ≤ 10 months.¹⁹⁶ 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 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 to 0.35; $P < .001$). No significant difference was seen in OS, although OS data were not mature at the time of final analysis for metastasis-free survival. Adverse events included rash (24% vs 5.5%), fracture (11% vs 6.5%), and hypothyroidism (8% vs 2%). Patients with M0 CRPC can be offered apalutamide, if PSADT is ≤ 10 months (category 1). In a prespecified exploratory analysis of SPARTAN, health-related QOL was maintained in both the apalutamide and placebo groups.¹⁹⁷

Chemotherapy and Immunotherapy

Recent research has expanded the therapeutic options for patients with metastatic CRPC depending on the presence or absence of symptoms.

Docetaxel

Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916).^{198–200} TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1,006 men.¹⁹⁹ 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.²⁰⁰ The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared with mitoxantrone plus prednisone.¹⁹⁸ Docetaxel is FDA-approved for metastatic CRPC. The standard regimen is every 3 weeks. An alternative to every-3-week docetaxel is a biweekly regimen of 50 mg/m². This regimen is based on a large randomized phase 2 trial of 346 men with metastatic CRPC randomized to either every-2-week docetaxel or every-3-week docetaxel, each with maintenance of ADT and prednisone.²⁰¹ Men 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.

Docetaxel is included as an upfront option for men with castration-naïve prostate cancer and distant metastases based on results from 2 phase 3 trials (ECOG 3805/CHAARTED and STAMPEDE).^{202,203} CHAARTED randomized 790 men with metastatic, castration-naïve prostate cancer to docetaxel (75 mg/m² intravenous every 3 weeks \times 6 doses) plus ADT or ADT alone.²⁰³ After a median follow-up 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; $P = .002$).²⁰⁴ 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; $P < .001$). Men with low-volume disease 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 3 trial, included patients with both M0 and M1 castration-naïve prostate cancer.²⁰² The results in the M1 population essentially confirmed the survival advantage of adding docetaxel (75 mg/m² intravenous every 3 weeks \times 6 doses) to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1,087 men 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). The results of the STAMPEDE trial seem to confirm the results of the CHAARTED trial.

Some data suggest that the use of docetaxel in combination with ADT and EBRT may benefit fit men with high- and very-high-risk localized disease. The GETUG 12 trial, which randomized 413 men with high- or very-high risk prostate cancer to IMRT and ADT or ADT, docetaxel, and estramustine.²⁰⁵ After a median follow-up of 8.8 years, 8-year relapse-free survival was 62% in the combination therapy arm and 50% in the ADT-only arm (adjusted HR, 0.71; 95% CI, 0.54–0.94; $P = .017$). The multicenter, phase 3 NRG Oncology RTOG 0521 trial randomized 563 patients with high- or very-high-risk prostate cancer ADT plus EBRT with or without docetaxel.²⁰⁶ After median follow-up 5.7 years, 4-year OS was 89% (95% CI, 84%–92%) for ADT/EBRT and 93% (95% CI, 90%–96%) for ADT/EBRT/docetaxel (HR, 0.69; 90% CI, 0.49 to 0.97; one-sided $P = .03$). Improvements were also seen in disease-free survival and the rate of distant metastasis. The panel does not recommend the addition of docetaxel to ADT plus EBRT in patients with high and very-high risk prostate cancer, however, at this time. Longer follow-up is needed to determine the effects of early docetaxel on response to subsequent treatment.

In addition, longer follow-up will show whether the long-term side effects of EBRT, which generally begin 4 to 5 years after EBRT, are increased with docetaxel.

Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semi-synthetic taxane derivative, for men with metastatic CRPC previously treated with a docetaxel-containing regimen. An international randomized phase 3 trial (TROPIC) randomized 755 men with progressive metastatic CRPC to receive cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m², each with daily prednisone.²⁰⁷ A 2.4-month improvement in OS was demonstrated with cabazitaxel compared with mitoxantrone (HR, 0.72; *P* < .0001). The improvement in survival was balanced against a higher toxic death rate with cabazitaxel (4.9% vs 1.9%), which was due, in large part, to differences in rates of sepsis and renal failure. Febrile neutropenia was observed in 7.5% of cabazitaxel-treated men vs 1.3% of mitoxantrone-treated men. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated men, 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.²⁰⁸ 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 progression-free survival and OS.²⁰⁹

The phase 3 open-label, multinational, noninferiority PROSELICA study compared 20 mg/m² cabazitaxel with 25 mg/m² cabazitaxel in 1,200 patients with metastatic CRPC who progressed on docetaxel.²¹⁰ 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. Cabazitaxel at 20 mg/m² every 3 weeks, with or without growth factor support, is now standard of care for fit patients. Cabazitaxel at 25 mg/m² may be considered for healthy men who wish to be more aggressive.

Recent results from the phase 3 FIRSTANA study suggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve metastatic CRPC.²¹¹ Median OS, the primary endpoint, was similar between 20 mg/m² cabazitaxel, 25 mg/m² cabazitaxel, and 75 mg/m² docetaxel (24.5, 25.2, and 24.3 months, respectively). Cabazitaxel was associated with lower rates of peripheral sensory neuropathy than docetaxel, particularly at 20 mg/m² (12% vs 25%). Therefore, patients who are not

candidates for docetaxel, who cannot tolerate docetaxel, or who have pre-existing mild peripheral neuropathy should be considered for cabazitaxel.²¹¹

Cabazitaxel should be given with concurrent steroids (daily prednisone or dexamethasone on the day of chemotherapy). Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pretreated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis), and symptom-directed antidiarrheal agents. Cabazitaxel was tested in patients with hepatic dysfunction in a small, phase I, dose-escalation study.²¹² 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.

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 3, multicenter, randomized, double-blind trial (D9902B),²¹³ in which 512 patients with minimally symptomatic or asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or placebo. Median survival in the vaccine arm was 25.8 months compared with 21.7 months in the control arm. 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.

The panel prefers that sipuleucel-T be used as initial therapy for asymptomatic or minimally symptomatic patients with metastatic CRPC, so that disease burden is lower and immune function potentially more intact. 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 use of pembrolizumab, an anti-PD1 antibody, for treatment of patients with “unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient solid tumors who have

progressed on prior treatment and who have no satisfactory alternative treatment options” on May 23, 2017.²¹⁴ The indication has since been expanded to include several cancer types, but not prostate cancer specifically.²¹⁵ The recommended adult dose of pembrolizumab for this indication is 200 mg intravenously once every 3 weeks.

FDA accelerated approval was based on the treatment of 149 patients across 5 clinical studies involving MSI-H or MMR-deficient (dMMR) colorectal (n=90) or noncolorectal (n=59) cancer for an objective response rate of 40% (59/149).²¹⁴ All patients received ≥ 1 prior regimen. Among the noncolorectal cohorts, 2 patients had metastatic CRPC: one attained a partial objective response, and the other attained stable disease for >9 months.

A limited number of additional patients with metastatic CRPC treated with pembrolizumab have been reported.^{59,216–218} In 1 study, only 1 patient had prostate cancer.²¹⁷ He had treatment-refractory, progressive, metastatic, dMMR disease and experienced a complete response; his prior therapy was not reported. In the other 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.²¹⁶ Some of the patients also had experienced disease progression on additional therapies (docetaxel for castration-naïve disease, abiraterone, and/or sipuleucel-T). Three of the 10 patients showed a near complete PSA response. Two of these 3 patients had radiographically measurable disease and showed 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 from 2 PSA responders and 2 PSA nonresponders revealed that one responder had an MSI-H tumor, whereas the other responder and the nonresponders did not. The non-randomized phase Ib KEYNOTE-028 trial included 23 patients with advanced, progressive prostate cancer, of whom 74% had received ≥ 2 previous therapies for metastatic disease.²¹⁸ The objective response rate by investigator review was of 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 median follow-up 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).

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

Based on the available data, the panel supports the use of pembrolizumab in patients with MSI-H or dMMR metastatic CRPC whose disease has progressed through at least 1 line of systemic therapy for M1 CRPC (category 2B). The prevalence of MMR deficiency in metastatic CRPC is estimated at 2%–5%,^{32,217} 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.

Treatment Implications for Patients With DNA Repair Gene Mutations

Early studies suggest germline and somatic mutations in homologous recombination repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.^{219–221} In particular, phase 2 data suggest that one PARP inhibitor, olaparib, has clinical activity in such patients, and trials of this agent and other PARP inhibitors are ongoing to assess the overall net clinical benefit of such therapy in men with CRPC, particularly in those men with either germline or somatically acquired DNA repair enzyme mutations.^{220,221} One of these trials was randomized, double-blind, and placebo-controlled, and the primary endpoint of median radiographic PFS was met (13.8 months in the olaparib/abiraterone arm vs 8.2 months in the placebo/abiraterone arm; HR, 0.65; 95% CI, 0.44–0.97; $P=.034$).²²¹ The 142 patients in this trial were not selected based on mutational status. At present, no PARP inhibitor is approved for use in prostate cancer.

DNA repair defects have been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.^{222–224} Platinum agents have shown some activity in patients with CRPC without molecular selection.²²⁵ Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

In addition, a recent study suggested that patients with metastatic CRPC and germline mutations in DNA repair genes may have better outcomes if treated with abiraterone or enzalutamide than with taxanes.³⁵ However, it should be noted that the response of patients with metastatic CRPC and homologous recombination repair gene mutations respond to standard therapies is similar to the response of patients without mutations.^{226,227}

The panel recommends clinical trial enrollment for men with prostate cancer and DNA repair gene mutations.

Agents Related to Bone Health in CRPC

In a multicenter study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every

3 weeks or placebo.²²⁸ At 15 months, fewer men in the zoledronic acid 4-mg group than men 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 days vs 321 days; $P=.01$).²²⁹ No significant differences were found in OS. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications. Earlier use of zoledronic acid in men with castration-naïve prostate cancer and bone metastases is not associated with lower risk for SREs, and in general should not be used for SRE prevention until the development of metastatic CRPC.²³⁰

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 men with bone metastatic CRPC treated with docetaxel alone or with zoledronic acid, 89Sr, or both.²³¹ 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 men with CRPC.²³² The absolute incidence of SREs was similar in the 2 groups; however, the median time to first SRE was delayed by 3.6 months by denosumab compared with zoledronic acid (20.7 vs 17.1 months; $P=.0002$ for 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). Most, but not all, patients who develop osteonecrosis of the jaw have preexisting dental problems.²³³

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Individual Disclosures for the NCCN Prostate Cancer Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Emmanuel S. Antonarakis, MD	None	Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Clovis Oncology; Dendreon Corporation; ESSA Pharmaceuticals; Janssen Pharmaceutica Products, LP; Medivation, Inc.; Merck & Co., Inc.; and sanofi-aventis U.S. LLC	None	Medical Oncology
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The NCCN Guidelines Staff have no conflicts to disclose.

^aThe following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:

Michael Hurwitz, MD, PhD: Pfizer Inc.

^bThe following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

Christopher J. Kane, MD, FACS: Stratify Genomics