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ADVANCED PROSTATE CANCER: AUA/SUO GUIDELINE (2023; AMENDED 2026)

Guideline Panel

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SUMMARY

Purpose

The management of advanced prostate cancer is rapidly evolving. To assist in clinical decision-making, evidence-based guideline statements were developed to provide a rational basis for evidence-based treatment. This guideline covers advanced prostate cancer, including disease stages that range from prostate-specific antigen (PSA) recurrence after exhaustion of local treatment options to widespread metastatic disease.

Methodology

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020.

In 2023, the Advanced Prostate Cancer guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines. The methodology team searched Ovid MEDLINE(R) ALL and the Cochrane Libraries for studies published between 2018, and March 16, 2022.

In 2026, the Advanced Prostate Cancer guideline was updated through the AUA amendment process. The methodology team searched PubMed for studies published between March 16, 2022 and August 26, 2025.

GUIDELINE STATEMENTS

EARLY EVALUATION AND COUNSELING

1. In patients with suspicion of advanced prostate cancer and no prior histologic confirmation, clinicians should obtain tissue diagnosis from the primary tumor or site of metastases when clinically feasible. (*Clinical Principle*)

2. Clinicians should discuss treatment options with advanced prostate cancer patients based on life expectancy, comorbidities, preferences, and tumor characteristics. Patient care should incorporate a multidisciplinary approach when available. (*Clinical Principle*)

3. Clinicians should optimize pain control or symptom support in advanced prostate cancer patients and encourage engagement with professional or community-based resources, including patient advocacy groups. (*Clinical Principle*)

4. For all patients with advanced prostate cancer, clinicians should offer germline testing. For patients with metastatic disease, somatic tumor testing should also be offered. (*Clinical Principle*)

BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE AFTER EXHAUSTION OF LOCAL TREATMENT OPTIONS

Prognosis

5. Clinicians should inform patients with PSA recurrence after exhaustion of local therapy regarding the risk of developing metastatic disease and follow such patients with serial PSA measurements and clinical evaluation. Clinicians may consider radiographic assessments based on overall PSA and PSA kinetics. (*Clinical Principle*)

6. In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases, clinicians should perform periodic staging evaluations consisting of imaging preferentially with prostate-specific membrane antigen positron emission tomography (PSMA PET) and/or computed tomography (CT), magnetic resonance imaging (MRI), and technetium bone scan. (*Clinical Principle*)

7. Clinicians should utilize PSMA PET imaging preferentially in patients with PSA recurrence after exhaustion of local therapy due to its greater sensitivity, or in the setting of negative conventional imaging. (*Expert Opinion*)

Treatment

8. For patients with a rising PSA after exhaustion of local therapy and no demonstrated metastatic disease, clinicians should risk stratify as low- or high-risk. High-risk patients generally are defined as patients with PSA doubling time (PSADT) ≤ 9 months. (*Clinical Principle*)

9. Androgen deprivation therapy (ADT) should not be routinely initiated for low-risk patients (PSADT > 9 months) with biochemical recurrence (BCR) after exhaustion of local therapy. (*Expert Opinion*)
    - For patients with a rising PSA after exhaustion of local therapy with low-risk features, including PSADT > 9 months, clinicians should offer observation and ADT should not be routinely initiated.
    - For patients with a rising PSA after exhaustion of local therapy with high-risk features, including PSADT ≤ 9 months, clinicians should offer ADT with enzalutamide.
    - For patients with a rising PSA after exhaustion of local therapy with high-risk features and no metastatic disease in whom ADT +/- androgen receptor pathway inhibitor (ARPI) is initiated, intermittent therapy may be offered in lieu of continuous therapy in the setting of a favorable response to therapy.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

Prognosis

10. Clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) in newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) patients. (*Clinical Principle*)

11. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) and stratify based on low- versus high-volume. High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases based on conventional imaging. (*Moderate Recommendation; Evidence Level: Grade B*)

12. Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. (*Moderate Recommendation; Evidence Level: Grade B*)

13. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic imaging. (*Clinical Principle*)

Treatment

14. Clinicians should offer ADT with either luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or surgical castration in patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade B*)

15. In addition to ADT, clinicians should also offer androgen pathway-directed therapy with abiraterone acetate plus prednisone, apalutamide, enzalutamide, or darolutamide to the majority of patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade A*)

16. In select mHSPC patients, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. (*Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B*)

17. In select mHSPC patients, clinicians may offer primary radiotherapy to the prostate in combination with ADT with or without an ARPI. (*Conditional Recommendation; Evidence Level: Grade C*)

18. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (*Strong Recommendation; Evidence Level: Grade A*)

19. In mHSPC patients with homologous recombination repair (HRR) gene alterations, particularly BRCA 2, clinicians may offer the combination of ADT, abiraterone, and niraparib. *(Expert Opinion)*

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

20. In non-metastatic castration-resistant prostate cancer (nmCRPC) patients, clinicians should obtain serial PSA measurements at three- to six-month intervals and calculate a PSADT starting at the time of development of castration-resistance. (*Clinical Principle*)

21. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional or PSMA PET imaging at intervals of 6 to 12 months. (*Expert Opinion*)

Treatment

22. Clinicians should offer apalutamide, darolutamide, or enzalutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (*Strong Recommendation; Evidence Level: Grade A*)

23. Clinicians may recommend observation with continued ADT to nmCRPC patients, particularly those at lower risk (PSADT >10 months) for developing metastatic disease. (*Clinical Principle*)

24. Clinicians should not offer systemic chemotherapy or immunotherapy to nmCRPC patients outside the context of a clinical trial. (*Clinical Principle*)

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

25. In metastatic castration-resistant prostate cancer (mCRPC) patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, lactate dehydrogenase [LDH], hemoglobin [Hgb], alkaline phosphatase level) and review location of metastatic disease (lymph node, bone, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision-making. (*Clinical Principle*)

26. In mCRPC patients without PSA progression or new symptoms, clinicians should perform imaging at least annually. (*Expert Opinion*)

Treatment

27. For most patients progressing to mCRPC who have not received prior ARPIs, clinicians should offer continued ADT with abiraterone acetate plus prednisone or enzalutamide. (*Strong Recommendation; Evidence Level: Grade A)*

28. In mCRPC patients with disease progression following treatment with an ARPI, clinicians should offer docetaxel. (*Strong Recommendation; Evidence Level: Grade B*)

29. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (*Conditional Recommendation; Evidence Level: Grade B*)

30. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm. (*Strong Recommendation; Evidence Level: Grade B*)

31. In mCRPC patients with disease progression following treatment with an ARPI (with or without prior docetaxel), and a positive PSMA PET/CT, clinicians should offer ^{177}Lu-PSMA-617. (*Strong Recommendation; Evidence Level: Grade B*)

32. In mCRPC patients who received prior docetaxel chemotherapy either in the mHSPC or mCRPC setting, clinicians may offer cabazitaxel. (*Conditional Recommendation; Evidence Level: Grade B*)

33. In mCRPC patients who received prior docetaxel chemotherapy and an ARPI, clinicians should recommend cabazitaxel rather than an alternative ARPI. (*Strong Recommendation; Evidence Level: Grade B*)

34. Clinicians may offer a poly (ADP-ribose) polymerase (PARP) inhibitor to select patients with deleterious germline or somatic HRR gene-mutated mCRPC who have progressed on prior ARPIs. Platinum-based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (*Conditional Recommendation; Evidence Level: Grade C*)

35. Clinicians may offer a PARP inhibitor in combination with an ARPI to select patients with deleterious germline or somatic HRR gene-mutated mCRPC. (*Conditional Recommendation; Evidence Level: Grade C*)

36. In patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) mCRPC, clinicians should offer pembrolizumab. (*Moderate Recommendation; Evidence Level: Grade C*)

BONE HEALTH

37. Clinicians should discuss the risk of osteoporosis associated with ADT and should assess the risk of fragility fracture in patients with advanced prostate cancer. (*Clinical Principle*)

38. Clinicians should recommend preventive treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to advanced prostate cancer patients on ADT. (*Clinical Principle*)

39. In advanced prostate cancer patients at high fracture risk due to bone loss, clinicians should recommend preventive treatments with bisphosphonates or denosumab and referral to physicians who have familiarity with the management of osteoporosis when appropriate. (*Clinical Principle*)

40. Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events. (*Moderate Recommendation; Evidence Level: Grade B*)

INTRODUCTION

METHODOLOGY

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Advanced Prostate Cancer Panel.

Panel Formation

The Panel was created in 2018 by the American Urological Association Education and Research, Inc. (AUAER). This guideline was developed in collaboration with the American Society for Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) with additional panel representation from the American Society of Clinical Oncology (ASCO). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members with specific expertise in this area in conjunction with ASTRO, SUO, and ASCO. Additionally, the Panel included patient representation. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

The 2023 Advanced Prostate Cancer Amendment Panel was created in 2022 by the AUA to review new literature and provide updates herein. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

The 2026 Advanced Prostate Cancer Amendment Panel was created in 2025 by the AUA to review new literature and provide updates herein. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

Searches and Article Selection

A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020. The methodology team supplemented searches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

The methodology team developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, and settings (PICOTS) of interest. The population was patients with advanced prostate cancer as described in **Table 3**. Treatments included first and second line antiandrogens, immunotherapy, chemotherapy, radiation therapy, surgery, radiopharmaceuticals, and surveillance

strategies. Comparisons were against placebo, no therapy or another active intervention, and intermittent versus continuous therapy. Outcomes included overall survival (OS), prostate cancer mortality, progression-free survival (PFS), prostate-specific antigen progression-free survival (PSA-PFS), failure-free survival, metastases-free survival, time to metastases, time to progression, skeletal events, and adverse events.

For evaluation of treatments, inclusion was restricted to randomized trials, with the exception of studies on sequencing of therapies for which cohort studies were also included. For evaluation of prognostic factors, the methodology team included primary studies and systematic reviews that reported hazard ratios (HR) or the area under the receiver operating characteristic curve (AUROC), a measure of discrimination. We excluded non-randomized studies of interventions and case reports, narrative reviews, case-control studies, and non-English language articles. We also excluded in vitro and animal studies. Articles were published in peer-reviewed journals in or after 1998, though the methodology team included studies published prior to 1998 that were identified from reference lists.

Using the pre-specified criteria, two investigators independently reviewed titles and abstracts of all citations. The methodology team used a two-phase method for screening full-text articles identified during review of titles and abstracts. In the first phase, methodologists reviewed full-text articles to identify relevant systematic reviews for inclusion. Methodologists selected systematic reviews that addressed Key Questions, were higher quality, and were published within the last five years. The second phase reviewed full-text articles to identify primary studies for key questions not sufficiently answered by previously published systematic reviews and new studies published subsequent to the systematic reviews.

Database searches resulted in 10,517 potentially relevant articles of which 918 were selected for full-text review; 230 publications met inclusion criteria and were included in this review. Forty-six studies were carried over from the prior AUA review.

Data Abstraction

For primary studies that met inclusion criteria, a single investigator abstracted information on study design, year, setting, country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (age, race, tumor stage, performance status, PSA level, prior treatments, type and extent of metastatic disease), results, and source of funding. For systematic reviews, investigators abstracted characteristics of the included studies (number, design and sample sizes of included studies, study settings), population characteristics (inclusion and exclusion criteria), interventions, methods and ratings for the risk of bias of included studies, synthesis methods, and results. For OS and PFS, HR estimates were based on the number of deaths or number of deaths or cases of progression, so that estimates <1 indicate improved survival. Data abstractions were reviewed by a second investigator for accuracy, and discrepancies were resolved through discussion and consensus.

Risk of Bias Assessment

Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For randomized trials and cohort studies, methodologists adapted criteria for assessing risk of bias from the United States (U.S.) Preventive Services Task Force.[1] Criteria for randomized trials included use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. For cohort studies on prognostic factors, criteria included methods for assembling cohorts, attrition, blinding assessment of outcomes, and adjustment for potential confounding.

The methodology team assessed systematic reviews using Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) criteria.[2] Criteria included use of pre-specified methods, appropriate search methods, assessment of risk of bias, and appropriate synthesis methods. Studies were rated as “low risk of bias,” “medium risk of bias,” or “high risk of bias” based on the presence and seriousness of methodological shortcomings.

Studies rated “low risk of bias” are generally considered valid. “Low risk of bias” randomized trials include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates (defined as >20%, not counting those who died or met other endpoints) and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated "medium risk of bias" are susceptible to some bias, though not necessarily enough to invalidate the results. These studies do not meet all the criteria for a rating of low risk of bias, but no flaw is likely to cause major bias. Studies may be missing information, making it difficult to assess limitations and potential problems. The "medium risk of bias" category is broad, and studies with this rating vary in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated "high risk of bias" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared interventions. The methodology team did not exclude studies rated high risk of bias a priori, but high risk of bias studies were considered to be less reliable than low or medium risk of bias studies, and the methodology team performed sensitivity analyses without high risk of bias studies to determine how their inclusion impacted findings.

Data Synthesis

The methodology team constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. The methodology team reported pooled estimates and other results from systematic reviews and examined whether the findings of new studies were consistent with the reviews.

The methodology team graded the strength of evidence for interventions using the approach described in the AHRQ EPC Methods Guide for Comparative Effectiveness and Effectiveness Reviews.[3, 4] For strength of evidence assessments, methodologists focused on the outcomes OS and PFS and key treatment comparisons. Strength of evidence assessments were based on the following domains:

- Study limitations, based on the overall risk of bias across studies (low, medium, or high) and the seriousness of methodological limitations
- Consistency of results across studies (consistent, inconsistent, or unable to determine when only one study was available)
- Directness of the evidence linking the intervention and health outcomes (direct or indirect)
- Precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (precise or imprecise)
- Reporting bias, based on whether the studies defined and reported primary outcomes and whether we identified relevant unpublished studies (suspected or undetected)

Determination of Evidence Strength

Based on assessments of the domains described above, the methodology team graded the strength of evidence for each intervention as high, moderate, low, or very low. Randomized controlled trials (RCT) of interventions start as "high" strength of evidence and are graded down based on the presence and severity of shortcomings in each domain. A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and could increase the confidence in the estimate. A "very low" grade indicates evidence either is unavailable or is too limited to permit any conclusion due to extreme study limitations, inconsistency, imprecision, or reporting bias.

The AUA employs a three-tiered strength of evidence system to underpin evidence-based guideline statements. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C. (**Table 1**)

The AUA categorizes body of evidence strength as Grade A (e.g., well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (e.g., RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (e.g., RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or

observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[5]

TABLE 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens. (**Table 2**) **Strong Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. **Moderate Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. **Conditional Recommendations** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, when benefits and harms are finely balanced, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens; therefore, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged.[6] A **Clinical Principle** is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. **Expert Opinion** refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and management of Advanced Prostate Cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from ASTRO, SUO, and ASCO as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 2-16, 2019 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and representation from prostate cancer advocacy to open the document further to the patient perspective. The draft guideline document was distributed to 96 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 44 reviewers provided comments, including 34 external reviewers. At the end of the peer review process, a total of 522 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD as well as the governing bodies of ASTRO and SUO for final approval.

The 2023 Advanced Prostate Cancer Amendment Panel was created in 2022 by the AUA. The AUA conducted a thorough peer review process and a call for peer reviewers was posted December 2022. The draft guidelines document was distributed to 89 peer reviewers, 38 of whom submitted comments. The Amendment Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC and SQC as well as SUO. It was then submitted to AUA Board of Directors for final approval.

The 2026 Advanced Prostate Cancer Amendment Panel was created in 2025 by the AUA. The AUA conducted a thorough peer review process and a call for peer reviewers was posted on the AUA website from January 6-23, 2026, to allow any additional interested parties to request a copy of the document for review. The draft guideline document was distributed to 134 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 44 reviewers provided comments, including 35 external reviewers. Once finalized, the guideline was submitted for approval to the original panel and the AUA PGC, SQC, and BOD as well as the governing body of SUO for final approval.

BACKGROUND

Epidemiology

Prostate cancer is the most common solid organ malignancy for men in the U.S. and remains the second leading cause of cancer deaths for this population. Approximately 333,830 new diagnoses of prostate cancer and 36,320 deaths are estimated in the U.S. in 2026.[7] The incidence of prostate cancer is 70% higher in Black men as compared to White men for reasons that remain unclear.[7] Importantly, the incidence of advanced stage disease including metastatic hormone-sensitive prostate cancer (mHSPC) has been increasing by about 5% per year in recent years. Unfortunately, prostate cancer mortality among Black men is approximately double that of men in most other groups. This disproportionate impact of prostate cancer morbidity and mortality on Black men is an area of active investigation that includes new approaches to screening, access to care, and treatment considerations among these men. [8] While metastatic prostate cancer remains a lethal disease, improvements in OS through combination therapies have resulted in a renaissance in the entire landscape for clinicians caring for men with advanced metastatic prostate cancer. Prostate cancer deaths are typically the result of progression to metastatic castration-resistant prostate cancer (mCRPC). Historically, the median survival for men with mCRPC was less than two years, but due to several factors, including the impact of novel therapies, the median survival is now increasing with some men surviving beyond five years.[9] Furthermore, rapid therapeutic advances in the treatment landscape for

mHSPC and mCRPC render treatment decisions and sequencing increasingly complex. Therefore, at present, there is limited data driven evidence regarding optimal agent combination or sequence. It is against this backdrop that the Panel provides evidence-based guidance for treatment of men with advanced prostate cancer and looks to the future with cautious optimism.

Justification for a New Guideline

Clinicians treating men with advanced prostate cancer are challenged with the rapidly evolving prostate cancer landscape given the approval of new classes of agents for use in various prostate cancer disease states. The increasing complexity of advanced prostate cancer management underscores the need for the current clinical practice guideline, developed to provide a rational basis for treatment of patients with advanced disease, based on currently available published data. To assist in clinical decision-making, guideline recommendations are furnished according to disease states across the entire continuum of advanced prostate cancer.

Disease States

This guideline covers advanced prostate cancer as defined by the five disease states outlined below. It should be noted that this guideline does not cover local therapy (see AUA Guideline on Clinically Localized Prostate Cancer).[10] The patient population covered in this guideline is assumed to have already received local or pelvic therapy, including adjuvant and salvage therapy (e.g., exhaustion of local treatment options). Further, neuroendocrine tumors and small cell variants were considered outside the scope of this guideline.

BIOCHEMICAL RECURRENCE ("RISING PSA STATE") WITHOUT METASTATIC DISEASE AFTER EXHAUSTION OF LOCAL TREATMENT OPTIONS

After local therapy including surgery and/or radiation, the first sign of recurrence is typically a rising PSA in the absence of visible metastases. This is also assuming that all forms of local therapy (e.g., salvage radiotherapy after radical prostatectomy, or salvage prostatectomy/salvage local ablative therapy after external beam radiotherapy [EBRT]) have been exhausted. Patients understand that their local treatment has not eradicated the cancer because of continued rises in PSA. Management of this disease state is controversial as evidence is lacking for optimal treatment approaches.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

mHSPC has been increasingly diagnosed since 2013, likely due to multiple factors including greater imaging sensitivity and changes to PSA screening guidelines, amongst other reasons. In addition to being increasingly common, mHSPC and treatment of this disease state has shifted greatly since the first studies (CHAARTED and STAMPEDE) testing up-front docetaxel were reported beginning in 2014.[11, 12] Metastatic hormone-sensitive disease can occur due to recurrence after initial local therapy for localized prostate cancer or as de novo metastatic disease, a distinction that may be useful when deciding upon systemic therapy. Additionally, the volume and site of metastatic disease are important factors that can affect prognosis and treatment choice.

CASTRATION-RESISTANT PROSTATE CANCER

Castration-resistant prostate cancer (CRPC), whether metastatic (mCRPC) or non-metastatic (nmCRPC), generally occurs in response to therapeutic pressure, specifically the use of androgen deprivation therapy (ADT). The exact mechanism of transition from hormone-sensitive to castration-resistant disease is still not fully understood, and some diseases may be inherently resistant at presentation. However, it is clear that despite castrate levels of androgens, the androgen receptor (AR) remains active and continues to drive prostate cancer progression in most cancers.[13, 14] Because of this, multiple agents have been developed that further decrease androgen production or block AR signaling in addition to standard ADT with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists. It is hypothesized that there are additional biologic pathways that function independently of androgen signaling resulting in CRPC. With a greater understanding of tumor biology, there is hope for continued development of innovative treatment options that further improve survival for men with CRPC.

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Men with a rising PSA but no visible metastatic disease on conventional imaging, despite medical or surgical castration, represent a uniquely distinct disease state. The advent of improved imaging including next generation positron emission tomography- computed tomography (PET-CT) scanning has allowed for the discovery of small

volume metastases that were previously undetected with standard clinical imaging such as bone scans, CT, and magnetic resonance imaging (MRI). Nevertheless, there remains a subset of patients whose disease remains defined by biochemical PSA rise only. Until recently, there have been no agents specifically FDA approved for the treatment of men with nmCRPC. However, three AR antagonists successfully prolonged metastasis-free survival (MFS), defined as the development of metastases or death from any cause, when compared with ADT plus placebo in men with nmCRPC.[15-17]

The use of MFS rather than OS as a regulatory endpoint is novel in solid tumors, and was partially based on the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) meta-analysis of 19 clinical trials demonstrating that MFS is a surrogate for OS in men with localized prostate cancer.[18] Additionally, recent press releases state that two of the three approved AR antagonists also improve OS in this population.[19, 20] Data from the third study continues to mature.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

The treatment of men with mCRPC has dramatically changed over the past decade. Prior to 2004, once primary androgen deprivation failed to control the disease, treatments were administered solely for palliation. Landmark studies by Tannock et al. and Petrylak et al. demonstrated that docetaxel improved survival and quality of life (QOL) for such patients with mCRPC.[21, 22] Since the approval of docetaxel, multiple additional agents that show a survival benefit have been FDA-approved on the basis of RCTs.[23-27] These agents have been tested in multiple "disease states" of mCRPC, both before and after docetaxel chemotherapy, to determine when patients might benefit from each treatment.

Terminology and Definitions

There are several key terms and definitions that should be considered when interpreting this guideline. First, **biochemical recurrence** is a rise in PSA in prostate cancer patients after treatment with surgery or radiation (PSA of 0.2ng/mL and a confirmatory value of 0.2ng/mL or greater following radical prostatectomy and nadir + 2.0ng/mL following radiation). This may occur in patients who do not have symptoms. **HSPC** refers to prostate cancer that has either not yet been treated with ADT or is still responsive to ADT as manifested by the absence of clinical progression, radiographic progression, or a rising PSA of ≥2.0ng/mL above nadir. This may also be referred to as castrate-sensitive prostate cancer, endocrine-sensitive prostate cancer, and hormone-naïve prostate cancer. **CRPC** is defined by disease progression despite ADT and a castrate level of testosterone (<50ng/dL). Contemporary lab testing indicates that testosterone levels decline to <20ng/dL after orchiectomy.[28] Progression may present as either a continuous rise in serum (PSA) levels (values identified at a minimum of 1 week intervals with estimations of PSA doubling time [PSADT] with at least 3 values measured ≥4 weeks apart), the progression of pre-existing or new radiographic disease, and/or clinical progression with symptoms. **High-volume metastatic disease** is used in the mHSPC setting, and is defined per the CHAARTED definition of the presence of visceral metastases and/or greater than or equal to four bone metastases with at least one outside of the vertebral column and pelvis.[11] **Low-volume metastatic disease** describes metastatic disease that does not meet high-volume criteria. These definitions can be useful when choosing treatment for mHSPC, particularly for radiation of the primary tumor, and are associated with better (low-volume) or poorer (high-volume) prognosis in the mHSPC disease state.[11, 29] **High-risk metastatic disease** is defined per the LATITUDE definition for mHSPC that has a poorer prognosis in the presence of 2 of the 3 following high-risk features: Gleason ≥ 8, ≥ 3 bone lesions, or measurable visceral metastases.[30] **De novo metastatic disease** describes metastatic disease that is present at the time of initial prostate cancer diagnosis rather than recurring after previous treatment of localized cancer. This is associated with poorer prognosis than recurrent disease.[31] **PSA doubling time** (PSADT) is the number of months required for the PSA value to increase two-fold.[32] There are a number of web-based tools available to calculate PSADT, including that provided by Memorial Sloan Kettering Cancer Center available at https://www.mskcc.org/nomograms/prostate/psa_doubling_time. This tool also provides supporting text detailing the precise calculation of PSADT. **Conventional imaging** is defined as CT, MRI, and ^{99m}Tc-methylene diphosphonate bone scan (bone scan). These terms are summarized in **Table 3**.

TABLE 3: Key Terminology

Term	Definition
Disease States	
Biochemical recurrence without metastatic disease	• a rise in PSA in prostate cancer patients after treatment with surgery or radiation (PSA of 0.2ng/mL and a confirmatory value of 0.2ng/mL or greater following radical prostatectomy and nadir + 2.0ng/mL following radiation); this may occur in patients who do not have symptoms
Hormone-sensitive prostate cancer	• prostate cancer that has either not yet been treated with ADT or is still responsive to ADT
Castration-resistant prostate cancer	• disease progression despite ADT and a castrate level of testosterone (<50ng/dL); progression may present as either a continuous rise in serum PSA levels (values identified at a minimum of 1-week intervals, with estimations of PSADT with at least 3 values measured ≥4 weeks apart), the progression of pre-existing or new radiographic disease, and/or clinical progression with symptoms
High-volume metastatic disease	• presence of visceral metastases and/or greater than or equal to four bone metastases with at least one outside of the vertebral column and pelvis
High-risk metastatic disease	• disease that has a poorer prognosis in the presence of two of the three following high-risk features: Gleason ≥8, ≥3 bone lesions, or measurable visceral metastases
De novo metastatic disease	• metastatic disease that is present at the time of initial prostate cancer diagnosis rather than recurring after previous treatment of localized cancer
Disease Management	
PSA doubling time	• the number of months required for the PSA value to increase two-fold
Conventional imaging	• computed tomography, magnetic resonance imaging, and ^{99m}Tc-methylene diphosphonate bone scan

Radiologic Considerations

The prostate cancer community has witnessed considerable developments in the detection of disease with next generation prostate cancer imaging. PET-CT has emerged as a sensitive and specific imaging test to detect prostate cancer metastases, particularly among men with BCR after primary therapy.[33] Multiple PET tracers have demonstrated promise in the evaluation of extent of prostate cancer including ^{18}F-fluciclovine, ^{18}F-sodium fluoride, ^{11}C-choline, and various tagged prostate-specific membrane antigen (PSMA) isoforms. While there is an emerging literature detailing the use of next generation imaging to guide management decisions in recurrent prostate cancer,[34, 35] there remains uncertainty about how these image-directed therapies will impact oncologic outcomes.

It is important for the practicing clinician to note that the studies underpinning this guideline's recommendations were largely predicated upon the use of conventional imaging including CT, MRI, and bone scan. As the medical evidence evolves to more consistently incorporate next generation imaging, the definition of 'non-metastatic' and 'metastatic' will evolve as likely will the definitions of "low-volume and high-volume" owing to the significant differences in sensitivity to detect metastatic disease between conventional and advanced imaging modalities.

Multidisciplinary Nature of Treatment in Today's Advanced Prostate Cancer Paradigm

As the therapeutic landscape evolves to include increasingly complex combinations of systemic therapies with or without local therapies, advances in imaging, and germline and somatic genetic testing, treating men with advanced prostate cancer is increasingly one that must embrace multidisciplinary management approaches. Team members should include urologists, medical oncologists, and radiation oncologists at a minimum when supporting treatment decisions for advanced disease.

Additional specialists may also include genitourinary pathology, genetic counseling, palliative care, and holistic specialists, as appropriate, in addition to primary care. Best practices must also include clinicians comfortable describing the use of germline and somatic genetic testing, and when advanced imaging techniques could be optimally used or avoided. Radiologists and nuclear medicine specialists are valuable in helping to accurately interpret scans. Palliative care team members may also play a key role when treating men with symptomatic metastatic disease. Palliative care itself is an interdisciplinary, holistic approach to managing an advanced disease such as prostate cancer with a guarded prognosis. It can include controlling symptoms that are physical, psychological, spiritual, and social. The goal of palliation is to prevent and relieve suffering and to support the best possible QOL for the patient and family.

Performance Status and Predicted Life Expectancy

Performance status and predicted life expectancy are both critical elements to incorporate into individualized clinical decision-making in men with advanced prostate cancer. Performance status remains a key factor in treatment decision-making, particularly among men with advanced prostate cancer. Indeed, performance status has been found to be strongly associated with survival among men with mCRPC,[36-39] and has been used to define index patients in prior versions of this guideline. Performance status generally describes an individual patient's level of functioning and how one's disease impacts a patient's activities of daily living. The first of two commonly used scales to evaluate performance status include the Eastern Cooperative Oncology Group (ECOG) scale from 0 to 5 where 0 is fully functional and 5 is dead. The second is the Karnofsky scale where 10 represents a moribund individual and 100 represents an individual with no limitations.

It is important to acknowledge that clinical trials have generally excluded patients with a poor performance status from participation. Thus, most data regarding management of patients with limited performance status are extrapolated from randomized trials of eligible patients who had a better performance status, as well as from some smaller trials and registries. Incorporating performance status into shared treatment decision-making permits the treating clinician and patient to characterize the balance of risk and benefit associated with sometimes morbid treatments. While performance status is frequently used to predict an individual patient's likelihood of tolerating a particular cancer treatment, it is equally important to consider the likelihood that a particular treatment improves disease-related symptoms and drives meaningful improvement in performance status.

Thoughtful assessment of performance status and life expectancy are essential components of evaluation and management of men with advanced prostate cancer. Indeed, assessment of performance status and life expectancy are core to establishing goals of care, incorporating individuals' values and preferences to best align available management options with what is most important to patients and their families. While performance status is no longer included in the classification of disease states in this guideline, ongoing assessment of performance status is considered a necessary component of continuing care that will help the patient and clinician guide the cascade of management for advanced prostate cancer.

Clinical Trial Enrollment

Clinicians should inform patients about suitable clinical trials and encourage patients to consider participation in such trials based on eligibility and access. Treatment options can be characterized as standard and as investigational (clinical trial). In general, standard therapies have proven efficacy and risks determined by prospective trials. There are many types of clinical trials including trials evaluating novel systemic, surgical, or radiation therapies; new approaches to approved therapies; device trials; and trials focusing on QOL and other patient outcomes. All clinical trials include specified aim(s) with a predetermined statistical plan. Institutional Review Boards approve all clinical trials and patient consent forms, and all patients must sign consent for trial participation.

In appropriate patients, clinical trial options should be considered, and trial options should be discussed with patients as part of the shared decision-making process. Clinical trials are listed by diagnosis and stage on the Clinicaltrials.gov website.

GUIDELINE STATEMENTS

EARLY EVALUATION AND COUNSELING

1. **In patients with suspicion of advanced prostate cancer and no prior histologic confirmation, clinicians should obtain tissue diagnosis from the primary tumor or site of metastases when clinically feasible. (*Clinical Principle*)**

Patients with clinical signs and symptoms suggestive of advanced prostate cancer should undergo a biopsy to obtain histologic confirmation at the time of diagnosis and at later dates, if needed. While biopsy of the metastatic deposit may be optimal, biopsy of the primary tumor may be all that is available. Although the clinical picture is often consistent with the diagnosis, subsequent treatment may strongly depend on histologic and molecular features of the malignancy. For example, PARP inhibitors[40] and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors[41] require the identification of mutations in DNA repair genes and evidence of mismatch repair (MMR) gene defects leading to microsatellite instability (MSI), respectively. Further, biopsy may reveal evidence of neuroendocrine differentiation. Additional treatments will be developed in the coming years that are biomarker-dependent. After treatment with standard ADT, the opportunity to obtain tissue may be delayed or lost. This recommendation comes with the caveat that patient safety always comes first, and if the patient cannot tolerate biopsy or if there is no accessible tissue, treatment may proceed in the absence of histological confirmation. A biopsy may be obtained later as the patient's clinical condition improves.

2. **Clinicians should discuss treatment options with advanced prostate cancer patients based on life expectancy, comorbidities, preferences, and tumor characteristics. Patient care should incorporate a multidisciplinary approach when available. (*Clinical Principle*)**

Prostate cancer patients frequently have comorbid conditions that may impact life expectancy as well as the ability to tolerate prostate cancer-directed therapies. High-quality care in advanced prostate cancer relies on shared decision-making that centers on patients' preferences and goals of care. For older patients or those with multiple comorbidities, a formal geriatric or medical assessment may provide assistance for the clinician in making management recommendations.

In the Panel's judgment, relevant input into these complex issues may be best obtained by the involvement of a number of prostate cancer experts (e.g., urology, medical oncology, palliative medicine, radiation oncology, mental health professionals) in addition to the patient's primary care provider in the care of patients with advanced prostate cancer.

3. **Clinicians should optimize pain control or symptom support in advanced prostate cancer patients and encourage engagement with professional or community-based resources, including patient advocacy groups. (*Clinical Principle*)**

While the focus on care for patients with metastatic disease is improving survival, management of patients' symptoms and QOL are of great concern to patients and their families. As such, physicians caring for patients with advanced disease should manage symptoms such as pain, urinary symptoms, and sexual function, as well as side-effects of treatment. In addition, providers should avail themselves of resources in the community such as in-person and online support groups, palliative care professionals, and mental health professionals who can provide additional support and improve QOL.

4. **For all patients with advanced prostate cancer, clinicians should offer germline testing. For patients with metastatic disease, somatic tumor testing should also be offered. (*Clinical Principle*)**

Germline testing should be considered for all patients with advanced prostate cancer, when possible, regardless of family or personal history of cancer. Several multigene panels evaluating cancer susceptibility genes are available. Germline mutations in genes involved in DNA damage repair (DDR) have been identified in 11.8% of men with metastatic prostate cancer, with the most commonly identified gene mutations being BRCA1/2, CHEK2, ATM, RAD51D, and PALB2.[42]

Germline testing may be used to counsel patients regarding their familial risk of associated malignancies. When possible, germline testing should include counseling by someone knowledgeable about the implications of testing. This may include a discussion of possible test results; implications for patients; discussion

of the Genetic Information Nondiscrimination Act (GINA); possible impact of test results on life, disability, and long-term care insurance; and potential role of cascade testing of family members if a pathogenic or likely pathogenic mutation is identified. Post-test counseling with a genetic counselor is necessary for anyone who is found to have one of these mutations. The Panel acknowledges that access to certified genetic counselors may be limited, particularly in community urology settings. Telehealth genetic counseling or provider-led counseling may facilitate recommended testing.

Somatic testing can be performed to identify DNA MMR status, MSI, tumor mutational burden (TMB), PTEN loss and other potential mutations that may inform prognosis and direct potential targeted therapies. Additionally, mutations in HRR genes such as BRCA1-2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L should be tested. These mutations may have implications in clinical trial eligibility or therapeutics selection (i.e., PARP inhibitors, immunotherapy, or possibly early use of cytotoxic chemotherapy).[43, 44] More recently, ctDNA is being explored for its potential role in guiding therapy in advanced prostate cancer, but tissue biopsy remains preferable for somatic testing.[45]

Finally, the landscape of evidence detailing the interactions between mutations and treatment individualization continues to evolve, and the use of genetic testing may ultimately enable the treating clinician to offer a personalized approach to prostate cancer treatment.

BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE AFTER EXHAUSTION OF LOCAL TREATMENT OPTIONS

Prognosis

5. **Clinicians should inform patients with PSA recurrence after exhaustion of local therapy regarding the risk of developing metastatic disease and follow such patients with serial PSA measurements and clinical evaluation. Clinicians may consider radiographic assessments based on overall PSA and PSA kinetics. (*Clinical Principle*)**

In the hormone-sensitive setting, PSA recurrence almost always precedes clinical detection of metastases.[46] However, given the indolent nature of some cancers, not all patients with a detectable PSA following primary treatment are destined to experience clinical recurrence or cancer-related death. The incidence of PSA recurrence after primary radical prostatectomy or radiotherapy varies depending on clinical and pathologic risk factors, such as tumor grade, stage, and pre-treatment PSA.[47-50]

A systematic review and meta-analysis showed that many of the risk factors for PSA recurrence (grade, stage, and pre-treatment PSA) were also prognostic factors for those who experience clinical recurrence.[51] In addition, time to PSA recurrence and PSADT were also associated with risk of subsequent metastases, prostate cancer-related death, and death from any cause. The authors of the systematic review proposed dichotomizing a patient's risk of metastases based on the most robust risk factors available in the literature. For patients with PSA recurrence after radical prostatectomy, International Society of Urologic Pathologists (ISUP) grade group 4/5 (Gleason ≥8) or PSADT ≤1 year were considered high-risk for development of metastases and death. For patients with PSA recurrence after prostate radiation, those with biopsy ISUP grade group 4/5 (Gleason ≥8) and/or those with ≤18 months to PSA failure are at highest risk. Patients who do not meet one of the criteria above are considered lower risk of developing clinical metastases.

The proposed risk stratification was recently applied to a European cohort of patients treated with radical prostatectomy.[52] In this analysis, the 5-year estimated freedom from metastases was 97.5% (95% CI: 95.8% to 99.1%) for the low-risk cohort and 86.7% (95% CI: 83.4% to 90.1%) for the high-risk cohort. Unfortunately, the discriminative accuracy was only 67% to predict metastases and 69% to predict prostate cancer-related death. Therefore, more work needs to be done to improve prognostication for patients with PSA recurrence, and the proposed risk strata have not yet been validated in a cohort treated with primary radiation.

Despite the limitations of risk assessment, it is clear that several factors predict future recurrence and that this information should be provided to patients. Since PSA kinetics contribute to the risk of clinical recurrence, serial PSA measurements and evaluations are necessary for patients who develop PSA recurrence after local therapy.

6. **In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases, clinicians should perform periodic staging evaluations consisting of imaging preferentially with PSMA PET and/or CT, MRI, and technetium bone scan. (*Clinical Principle*)**

Cross-sectional imaging with CT or MRI along with ^{99m}Tc-methylene diphosphonate bone scintigraphy have been the standard imaging approaches for post-treatment BCR. The primary rationale for utilizing these approaches relates to the fact that current standard of care (SOC) systemic treatments in mHSPC are based on such conventional imaging approaches rather than advanced/molecular imaging (e.g., CHAARTED, STAMPEDE, LATITUDE). It should be noted, however, that these modalities infrequently detect metastases in the setting of early PSA recurrence (e.g., PSA <5ng/mL).[53-55] Historically, Kane et al. and colleagues reported that only 14% of patients in a BCR cohort had positive CT scans and 9.4% had positive bone scans, with these patients generally having high PSAs and/or rapid PSA kinetics.[53] Only 4.5% of patients with a PSA <10ng/mL had a positive bone scan. Odewole et al. reported on a cohort of patients undergoing both CT and ^{18}F-fluciclovine PET for BCR, and found that 6 of 29 patients (20.7%) with a PSA ≤5ng/mL had a positive CT finding.[54] In another study, the CT detection rate was 17% for patients with a PSA ≤4ng/mL.[55] Novel imaging techniques have evolved, and there are now several FDA approved PSMA PET agents for patients with advanced prostate cancer (^{68}Ga-PSMA-11,Piflufolastat F-18 [^{18}F-DCFPyL], and f-18-flotuflolastat [18f-rh-PSMA-7.3]),[56-59] including patients with suspected recurrence based on rising PSA levels, which demonstrate greater sensitivity than conventional imaging.

7. **Clinicians should utilize PSMA PET imaging preferentially in patients with PSA recurrence after exhaustion of local therapy due to its greater sensitivity, or in the setting of negative conventional imaging. (*Expert Opinion*)**

PET tracers show greater sensitivity than conventional imaging for the detection of prostate cancer recurrence and metastases at low PSA values (<2.0ng/mL). Historically, ^{18}F-fluciclovine was one of the initially available radiotracers in the U.S., imaging amino acid metabolism. The detection of prostate bed recurrences and nodal metastases in patients with biochemically recurrent disease with PSA values still below 1.0 varies between 21% and 72%, respectively.[54, 60] The detection rate appears dependent upon both PSA kinetics and histologic grade. The smallest short-axis diameter of nodes exhibiting uptake is reported at between 4 and 9mm, superior to CT. The detection of osseous metastases by ^{18}F-fluciclovine appears comparable to standard bone scintigraphy although studies are limited.

Since the publication of the last guideline, there has been a shift in clinical practice to preferentially obtain PSMA PET CT imaging in patients with BCR. This is based on the fact that the FDA has approved several PET agents for the management of advanced prostate cancer, ^{68}Ga-PSMA-11,^{18}F-DCFPyL, and ^{18}F-rhPSMA-7.3.[56-59] PSMA is a transmembrane protein highly overexpressed in over 90% of prostate cancers. ^{68}Ga-PSMA-11 is a radiolabeled small molecule that binds to the PSMA receptor. It has high specificity and sensitivity and outperforms standard CT and MRI in detection of nodal and osseous metastases.[61, 62] In a recent prospective study of men who had undergone prostatectomy and had a rising PSA still under 2.0ng/mL, PSMA PET detected occult metastases significantly more frequently than fluciclovine-PET with an odds ratio over 4.[63] ^{18}F-DCFPyL, another small molecule that binds to the extracellular domain of PSMA with high affinity, was shown to have a correct localization rate of 84.8% to 87.0% in a study of 208 men with rising PSA and negative conventional imaging following curative intent surgery or radiotherapy.[64] Both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL are indicated for patients with suspected prostate cancer metastasis considering surgery or radiation therapy and also indicated for patients with suspected prostate cancer recurrence based on elevated serum PSA levels. The role of PSMA PET in assessing indications and response for metastatic patients is still under investigation. Additional PSMA agents are also currently under investigation. PET agents such as ^{11}C-choline have FDA approval but are no longer in routine use for prostate cancer due to lower sensitivity and specificity for metastatic disease compared to other agents.[60] Further, the short half-life of ^{11}C-choline requires that it be manufactured on site, so it is impractical for most centers.

While advanced imaging tests may enhance detection of metastatic lesions, the impact on patients and OS has yet to be fully demonstrated. It is still unclear what may be gained by the early detection of recurrent disease. In

instances of planned salvage radiation therapy or salvage lymphadenectomy, the treatment templates may be adjusted as a result of PSMA PET imaging findings. In addition, oligometastatic disease may be identified, and such patients may be offered enrollment in clinical trials. While such approaches may be intuitively appealing, to date there is a limited amount of evidence suggesting benefit in terms of a delay in disease progression (ORIOLE),[65] improvement in ADT-free survival (STOMP) or improvement in OS (SABR-COMET).[66] To date, there is limited evidence that metastasis-directed therapy (MDT) confers a survival benefit.[67]

Treatment

8. **For patients with a rising PSA after exhaustion of local therapy and no demonstrated metastatic disease, clinicians should risk stratify as low- or high-risk. High-risk patients generally are defined as patients with PSADT ≤ 9 months. (*Clinical Principle*)**

In men with BCR following definitive local therapy, PSADT is among the most powerful predictors of subsequent metastasis and prostate cancer–specific mortality. Shorter PSADT reflects more aggressive tumor biology and consistently stratifies patients into distinct risk categories. Multiple retrospective cohorts have demonstrated that PSADT independently predicts metastasis after radical prostatectomy and radiation therapy, even after adjustment for Gleason grade and pathologic stage. Accordingly, contemporary guidelines incorporate PSADT into risk stratification schemas to guide intensity of surveillance, timing of advanced imaging (e.g., PSMA PET), and consideration of systemic therapy in high-risk BCR.

9. **ADT should not be routinely initiated for low-risk patients (PSADT > 9 months) with BCR after exhaustion of local therapy. (*Expert Opinion*)**

    - For patients with a rising PSA after exhaustion of local therapy with low-risk features, including PSADT > 9 months months, clinicians should offer observation and ADT should not be routinely initiated.
    - For patients with a rising PSA after exhaustion of local therapy with high-risk features, including PSADT ≤ 9 months, clinicians should offer ADT with enzalutamide.
    - For patients with a rising PSA after exhaustion of local therapy with high-risk features and no metastatic disease in whom ADT +/- ARPI is initiated, intermittent therapy may be offered in lieu of continuous therapy in the setting of a favorable response to therapy.

In men with high-risk BCR (PSADT ≤ 9 months) after definitive local therapy, the phase III EMBARK trial randomized patients 1:1:1 to enzalutamide plus leuprolide, enzalutamide monotherapy, or leuprolide plus placebo within a protocol incorporating planned intermittent therapy (“drug holiday”). In these high-risk patients, enzalutamide plus leuprolide or enzalutamide alone may be offered after radical prostatectomy with a PSA ≥ 1.0 ng/mL or PSA ≥ 2.0 ng/mL above nadir after radiotherapy. In the EMBARK study, eligibility was based on conventional imaging.[68-70] Treatment could be suspended if PSA declined below a prespecified nadir threshold (e.g., <0.2 ng/mL at week 36), with reinitiation triggered by protocol-defined PSA rises. The primary endpoint, metastasis-free survival (MFS), was significantly improved with enzalutamide plus leuprolide versus leuprolide alone (5-year MFS approximately 87.3% versus 71.4%; HR ~0.42), and enzalutamide monotherapy also improved MFS (HR ~0.63). Updated results demonstrated a significant OS benefit for the combination arm versus ADT alone (approximately 78.9% versus 69.5% 8-year OS; HR ~0.60), confirming durable benefit with early intensified androgen receptor inhibition within a PSA nadir-guided intermittent framework.

The PRESTO (AFT-19) trial[71] enrolled men with high-risk BCR after prostatectomy and adjuvant or salvage radiotherapy and a short PSADT (≤9 months), randomizing patients to a finite 52-week course of ADT alone, ADT plus apalutamide, or ADT plus apalutamide plus abiraterone/prednisone, followed by structured observation. This design intentionally incorporated treatment cessation after completion of therapy, with PSA nadir and subsequent PSA rises defining progression endpoints. Both intensified regimens significantly prolonged PSA-PFS compared with ADT alone (median PSA-PFS approximately 24.9–26.0 months versus 20.0–20.3 months; HRs ~0.48–0.52), without significant delays in testosterone recovery. Mature metastasis-free and OS outcomes are pending, but these data support finite intensified androgen blockade guided by PSA kinetics in high-risk BCR.

In addition, data from historical studies using ADT monotherapy further support the role of intermittent therapy. One RCT demonstrated the safety of an intermittent approach. An open-label trial by Crook et al. (n=1,386) compared intermittent versus continuous ADT in patients with a PSA rise to >3ng/mL more than 1 year following primary or salvage radiotherapy for localized prostate cancer.[72] An important limitation of this study to note is the lack of any stratifying criteria or initial risk factors. Intermittent therapy consisted of an eight-month treatment cycle. At the end of the 8-month cycle, treatment was discontinued if there was no evidence of clinical disease progression, the PSA level was <4ng/mL and did not increase more than 1ng/mL. It is further noted that the PSA threshold to reinitiate the next cycle of ADT was a level of 10ng/mL. At a median follow-up of 6.9 years, there was no difference in survival between intermittent versus continuous ADT (median 8.8 versus 9.1 years, (HR=1.02; 95% CI: 0.86 to 1.21), meeting the predefined non-inferiority threshold. There was also no difference in prostate cancer-specific survival (HR=1.18; 95% CI: 0.90 to 1.55). Intermittent therapy was associated with better scores for hot flashes (p<0.001), desire for sexual activity (p<0.001), and urinary symptoms (p=0.006) compared with continuous therapy.

Another open-label EC507 trial (n=109) study compared intermittent versus continuous ADT in patients with a PSA increase to ≥1ng/mL following an initial decrease to <0.5ng/mL within 3 months of radical prostatectomy.[73] All patients underwent induction with leuprorelin acetate, and patients who achieved a PSA level <0.5ng/mL during induction were randomized to intermittent versus continuous ADT. In the intermittent therapy arm, ADT was resumed if PSA levels increased to ≥3ng/mL. The primary outcome of the trial was testosterone recovery, which was achieved in 79.3% of patients in the first intermittent ADT cycle and 64.9% during the second intermittent ADT cycle. There was no difference between intermittent versus continuous ADT in time to castration resistance (mean 976 versus 986 days, p=0.85); OS and PFS were not reported.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

Prognosis

10. Clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) in newly diagnosed mHSPC patients. (*Clinical Principle*)

The presence and extent of metastatic disease play a central role in determining which and if any therapy is beneficial. Patients without metastatic disease have not been shown to benefit from aggressive systemic therapy. Further, clinicians should categorize patients as de novo metastatic disease or having progression in stage after prior failed treatment. Studies of systemic therapy have demonstrated that extent of metastatic disease influences response. For example, STAMPEDE demonstrated that only the subset of men with low-volume disease showed an improvement in survival with radiotherapy to the prostate in combination with ADT.[74] As a result, presence of metastatic disease, its burden, and precise locations should be assessed prior to treatment.

Patients diagnosed with higk-risk cancer defined by D'Amico risk factors (cT3a or greater, Grade Group 4/5, or PSA>20ng/mL) should undergo routine bone scan and cross-sectional imaging (CT or MRI) or PET imaging at the time of diagnosis. PSMA PET availability is increasing in the U.S. and detects metastatic disease at low PSA values. As outlined above, the extent and location of metastasis should be documented. Imaging should be repeated for men who undergo treatment at the time of PSA failure. It is notable that the median PSA at which metastasis is detected after curative intent is highly variable in some studies with a median of 31ng/mL and a range of 0.2 to 798.5ng/mL.[75] Factors associated with rapid progression to metastatic disease include short PSADT, a high pathologic or biopsy Gleason score after radical prostatectomy, and a short interval to biochemical failure.[51] In addition, it is notable that men with de novo metastases appear to do worse than men who develop metastatic disease subsequent to radiation or surgery. It is unknown if this is due to a therapeutic effect, lead time bias, or ascertainment bias.

PET imaging detects metastatic disease at low PSA values and, therefore, has changed our ability to identify low-volume metastatic disease. ^{18}F-Fluciclovine is

available and approved for patients for whom local therapy fails to control disease. Men with PSA over 1.0ng/mL were found to have avid lesions in 57% of cases.[76] ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, and ^{18}F-rhPSMA-7.3 are indicated for patients with suspected prostate cancer metastasis considering local therapy and as well as for patients with suspected prostate cancer recurrence based on elevated serum PSA levels. Utilization of PSMA PET may lead to the diagnosis of metastatic disease not previously detected with conventional imaging. While this detection of metastases at lower PSA levels is helpful in guiding therapy, it is important to note that the clinical trials for treatment did not use PET imaging; therefore, it is unknown if volume of disease on PET imaging can accurately classify patients into high- and low-risk groups.

11. **In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) and stratify based on low- versus high-volume. High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases based on conventional imaging. (*Moderate Recommendation; Evidence Level: Grade B*)**

The presence and extent of metastatic disease play a central role in determining which and if any therapy is beneficial. Patients without metastatic disease have not been shown to benefit from aggressive systemic therapy. Further, clinicians should categorize patients as de novo metastatic disease or having progression in stage after prior failed treatment. Studies of systemic therapy have demonstrated that extent of metastatic disease influences response. For example, STAMPEDE demonstrated that only the subset of men with low-volume disease showed an improvement in survival with radiotherapy in combination with ADT.[74] As a result, presence of metastatic disease, its burden, and precise locations should be assessed prior to treatment. While this detection of metastases at lower PSA levels is helpful in guiding therapy, it is important to note that the clinical trials for treatment did not use PET imaging; therefore, it is unknown if volume of disease on PET imaging can accurately classify patients into high- and low-risk groups.

Patients diagnosed with aggressive cancer defined by D'Amico risk factors (cT3a or greater, Grade Group 4/5, or PSA>20ng/mL) should undergo routine bone scan and cross-sectional imaging (CT or MRI) or PET imaging at the time of diagnosis. PSMA PET availability is increasing in the U.S. and detects metastatic disease at low PSA values. As outlined above, the extent and location of metastasis should be documented. Imaging should be repeated for men who undergo treatment at the time of PSA failure. It is notable that the median PSA at which metastasis is detected after curative intent is highly variable in some studies with a median of 31ng/mL and a range of 0.2 to 798.5ng/mL.[75] Factors associated with rapid progression to metastatic disease include short PSADT, a high pathologic or biopsy Gleason score after radical prostatectomy, and a short interval to biochemical failure. In addition, it is notable that men with de novo metastases appear to do worse than men who develop metastatic disease subsequent to radiation or surgery. It is unknown if this is due to a therapeutic effect, lead time bias, or ascertainment bias.

PET imaging detects metastatic disease at low PSA values and, therefore, has changed our ability to identify low-volume metastatic disease. ^{18}F-Fluciclovine is available and approved for patients for whom local therapy fails to control disease. Men with PSA over 1.0ng/mL were found to have avid lesions in 57% of cases.[76] ^{68}Ga-PSMA-11, rh-PSMA-7.3 and ^{18}F-DCFPyL are indicated for patients with suspected prostate cancer metastasis considering local therapy and as well as for patients with suspected prostate cancer recurrence based on elevated serum PSA levels.[56-59] Utilization of PSMA PET may lead to the diagnosis of metastatic disease not previously detected with conventional imaging.

12. **Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. (*Moderate Recommendation; Evidence Level: Grade B*)**

Symptoms in mHSPC have been shown to have prognostic value. In addition, understanding cancer-related symptoms is key to optimizing pain and other symptom management in addition to anti-cancer therapy. In an analysis of patients in the SWOG 8894 trial, presence of bone pain (adjusted OR=2.61; 95% CI: 1.66 to 4.12) was among the factors associated with poorer 10-year survival.[77]

13. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic imaging. (*Clinical Principle*)

The use of PSA as an instrument of evaluation in metastatic prostate cancers is common practice. In most reported studies, PSA is a measured variable and recorded at several time points at diagnosis and during treatment (baseline, induction [after a defined period of therapy], serial monitoring, and at progression). In many studies, PSA has demonstrated clear prognostic value and is used in many of the risk classification systems. In the SWOG 8894 trial, a comparison of bilateral orchiectomy with or without flutamide for treatment of metastatic prostate cancer, many clinical factors were analyzed in the assessment of risk including the finding that a higher PSA (adjusted OR=1.18 for log PSA; 95% CI: 1.03 to 1.34) was associated with poorer 10-year survival.[77]

Studies using the SEER registry database have found higher PSA is associated with worse cancer-specific survival (PSA <60 versus ≥60: HR=0.624; 95% CI: 0.535 to 0.727).[78] Additionally, for studies showing prognostic risk group stratification, PSA or PSA metrics are consistent variables in determination of group assignment.[79-81]

PSA decline after initiation of ADT (nadir) has been shown to be prognostic based on several studies and is useful in patient counseling. It is also likely useful in risk stratification for clinical trials. There are several prospective studies that have demonstrated the power of the PSA nadir in risk stratification. In an early analysis of SWOG 9346 looking at intermittent ADT in patients with metastatic prostate cancer, results demonstrated that PSA nadir at 7 months, ≤4ng/mL versus >4ng/mL, risk stratified patients receiving ADT, showing median survivals of 69 months versus 16 months, p<0.0001.[82] This was followed by a later analysis of SWOG 9346 trial demonstrating that PSA nadir after six to seven months of ADT in newly diagnosed metastatic prostate cancer patients was prognostic for survival. An initial analysis demonstrated 3 prognostic groups could be identified based on PSA nadir; PSA >4, PSA 0.2 to 4, and PSA <0.2 with median survivals of 13 months, 44 months, and 75 months, respectively (p<0.001).[83] Obtaining PSA at three- to six-month intervals allows for determination of the nadir and risk group stratification, and assists in patient counseling and setting expectations. With the changes in systemic therapy combinations, it is important to validate the prognostic value of nadir in more contemporary systemic settings. A recent analysis of the CHAARTED study showed PSA nadir at 7 months was a strong prognostic factor for OS when comparing nadirs ≤0.2ng/mL versus >4ng/mL (60.4 months versus 22.2 months, p<0.001).[84] Similar analyses are being explored from RCTs previously evaluating abiraterone acetate as well as second generation AR targeted therapies to determine if the prognostic value will hold true with more potent androgen axis therapies.

PSA has also been used for determination of treatment changes or alterations based on the belief that it provides insight as a measure of adequate response and in defining progression to castration resistance. There is no general consensus, but consideration for the use of PSA for defining an adequate response include length of initial treatment if induction of intermittent ADT is being considered as well as timing of re-initiation of therapy. PSA is also used in identifying CRPC, which includes a definition of rising PSA in the setting of a castrate level of testosterone. Definitions of CRPC are variable, but a common one is from the Prostate Cancer Working Group, which is now on the third version of a consensus on CRPC progression. This includes measuring PSA and identifying rising values at a minimum of 1-week intervals with a minimal value of 2.0ng/mL, with estimations of PSADT with at least 3 values measured ≥4 weeks apart.[85] Use of periodic testosterone measurement may also be used to confirm response to ADT.

There is clearly a consistent use of PSA and PSA metrics in the evaluation and risk stratification for men with HSPC; therefore, the recommendation for obtaining baseline levels and values every three to six months for monitoring is practical. Clinicians should be aware, however, that PSA alone is not completely predictive of cancer progression as some patients may demonstrate cancer growth in the absence of a PSA rise. This is particularly true in poorly differentiated, ductal, and neuroendocrine tumors as well as mCRPC. Symptom assessment is an important adjunct in these cases. Given that metastatic disease can progress in these patients even with relatively stable PSAs, periodic imaging is reasonable to assess disease stability.

There is no set interval for imaging of men with mHSPC, but imaging can demonstrate progression in the absence

of PSA changes or in the absence of symptoms and should be considered as a method of evaluation of these patients. Imaging can include PSMA PET or conventional imaging (CT, MRI, bone scan).

Treatment

14. Clinicians should offer ADT with either LHRH agonists or antagonists or surgical castration in patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade B*)

The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins et al. in the 1940s.[42] Castrate levels of testosterone (<50ng/dL) may be achieved with LHRH analogues, gonadotropin-releasing hormone (GnRH) antagonists, or orchiectomy. These treatments are considered equivalent in cancer control, although they have never been compared in large RCTs. GnRH antagonists and orchiectomy as monotherapy have a rapid onset of action and avoid the 'testosterone flare' seen with LHRH analogues alone making them useful in situations needing rapid hormone ablation such as impending spinal cord compression.

At the time of initial publication of this guideline, the methods for achieving castrate levels of testosterone were either surgical or injectable. On December 18, 2020, the FDA approved relugolix as the first oral GnRH receptor antagonist for adult patients with advanced prostate cancer.[86] Approval was based on the phase III HERO study that showed favorable testosterone suppression and adverse effects of oral relugolix (120mg/day) compared to leuprolide.[87]

15. In addition to ADT, clinicians should also offer androgen pathway-directed therapy with abiraterone acetate plus prednisone, apalutamide, enzalutamide, or darolutamide to the majority of patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade A*)

For mHSPC remains an incurable manifestation of the disease. While ADT, with or without non-steroidal antiandrogens, has been the backbone of mHSPC treatment for many decades, ADT alone is no longer considered sufficient treatment for mHSPC. Multiple studies have shown that additional therapy significantly extends OS and PFS in mHSPC patients.

ABIRATERONE ACETATE

Abiraterone acetate, an androgen biosynthesis inhibitor, is a non-steroidal irreversible inhibitor of CYP17A1, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA, and androstenedione.[88] In essence, abiraterone acetate is similar to ADT, but it is more potent, inhibiting gonadal and extragonadal androgen synthesis.

In the double-blind, placebo-controlled, phase III LATITUDE trial, 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate (1,000mg given once daily as four 250mg tablets) plus prednisone (5mg daily) or ADT plus placebo. The primary endpoints were OS and radiographic PFS (rPFS). After a median follow-up of 30.4 months at a planned interim analysis, the median OS was significantly longer in the abiraterone acetate group than in the placebo group (not reached versus 34.7 months) (HR=0.62; 95% CI: 0.51 to 0.76; p<0.001). The median length of rPFS was 33.0 months in the abiraterone acetate group and 14.8 months in the placebo group (HR=0.47; 95% CI: 0.39 to 0.55; p<0.001). Updated results continue to confirm benefit in this trial. The final analysis of this trial, at a median follow-up of 51.8 months, OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI: 48.2 to not reached]) compared to the placebo group (36.5 months [33.5 to 40.0]), with an HR of 0.66 (95% CI: 0.56 to 0.78; p<0.0001).[89]

In the STAMPEDE trial,[90] 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1,000mg daily) and prednisolone (5mg daily). A total of 52% of patients had metastatic disease. The primary outcome was OS. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT group (HR=0.63; 95% CI: 0.52 to 0.76; p<0.001); the HR was 0.61 in those with metastatic disease.

Abiraterone acetate can elevate liver enzyme levels, and should be avoided in patients where liver toxicity is a concern. As such, clinicians should monitor liver enzymes as well as potassium levels. Adverse events in the LATITUDE trial included mineralocorticoid-related hypertension (20%) and hypokalemia (10%). Further, the use of a steroid in combination with treatments for metastatic disease may require additional considerations for patients with comorbid conditions, such as diabetes or significant osteoporosis.

APALUTAMIDE

Apalutamide is an ARPI. This oral agent acts as an AR inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription.[91] In the double-blind, phase III TITAN study,[92] 525 patients were assigned to receive apalutamide (240mg daily) with ADT compared to 527 patients receiving placebo plus ADT. Primary endpoints included rPFS and OS. At a median of 22.7 months follow-up, the percentage of patients with rPFS at 24 months was 68.2% in the apalutamide group compared to 47.5% in the placebo group (HR=0.48; 95% CI: 0.39 to 0.60; p<0.001). OS at 24 months was greater with apalutamide compared to placebo (82.4% versus 73.5%; HR=0.67; 95% CI: 0.51 to 0.89; p=0.005). At the time of final analysis (44.0 months median follow-up), a total of 405 deaths had occurred (170 in the apalutamide arm, 235 in the placebo arm). An improvement in median OS was observed: not reached in the apalutamide group versus 52.2 months in the placebo group (HR=0.65; 95% CI: 0.53 to 0.79; p<0.0001), with a 35% reduction in risk of death.[93] Rash of any grade was more common among patients who received apalutamide compared to those who received placebo (27.1% versus 8.5%) including the risk of Stevens-Johnson syndrome/toxic epidermal necrolysis.[94]

ENZALUTAMIDE

Enzalutamide is an ARPI. It is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the AR, DNA-binding and coactivator recruitment.[95] In the open-label, randomized, phase III ENZAMET trial,[96] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide (160mg daily) or a standard non-steroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide—standard care). The primary end point was OS. With a median follow-up of 34 months, there were 102 deaths in the enzalutamide group compared to 143 deaths in the standard care group (HR=0.67; 95% CI: 0.52 to 0.86; p=0.002). Kaplan-Meier estimates of OS at 3 years were 80% in the enzalutamide group and 72% in the standard care group.

Discontinuation of treatment due to adverse events was more frequent in the enzalutamide group (33 events versus 14 events, respectively). Fatigue was more common in the enzalutamide group, and seizures occurred in 7 patients in the enzalutamide group (1%) compared to 0 patients in the standard care group. In this trial, approximately 16% of patients also received docetaxel and this study did not impact the observed benefit of enzalutamide. This trial did not address the role of early intensification by adding docetaxel to enzalutamide.

In the double-blind, phase III ARCHES trial, Armstrong et al. randomly assigned 1,150 men with mHSPC in a 1:1 ratio to receive either enzalutamide (160mg per day) or placebo. All patients also received ADT. The primary endpoint was rPFS. As of October 2018, the risk of rPFS or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (median not reached versus 19.0 months; HR=0.39; 95% CI: 0.30 to 0.50; p<0.001). Similar improvements were also seen in risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration-resistance, and reduced risk of pain progression. In an update on this trial, the final pre-specified analysis of OS, which was a key secondary end point, and an update on rPFS was reported. Following unblinding, 180 (31.3%) progression-free patients randomly assigned to placebo plus ADT crossed over to open-label enzalutamide plus ADT. At a median follow-up of 44.6 months, 154 of 574 patients randomly assigned to enzalutamide plus ADT and 202 of 576 patients randomly assigned to placebo plus ADT had died. Enzalutamide plus ADT reduced risk of death by 34% versus placebo plus ADT (median not reached in either group; HR=0.66; 95% CI: 0.53 to 0.81; p<0.001).[97]

DAROLUTAMIDE

Darolutamide is an ARPI. The ARANOTE trial[98] was a global, phase III trial that randomized 669 patients with mHSPC to ADT with darolutamide versus ADT with placebo in a 2:1 ratio. Darolutamide 600mg was given twice daily. Primary endpoint was rPFS. After median follow-up of 25 months, rate of radiographic progression was 28.7% in the darolutamide groups versus 42.2% in the placebo group. Darolutamide plus ADT significantly improved rPFS (HR 0.54; 95% CI: 0.41 to 0.71; p<0.0001). There was also delayed time to mCRPC (HR 0.40; 95% CI: 0.32 to 0.51) and time to pain progression (HR=0.72; 95% CI: 0.54 to 0.96). At the primary cutoff date, difference in OS was not significant but favored darolutamide. Tolerability was similar between groups and rates of fatigue was lower in patients who received darolutamide versus placebo (5.6% versus 8.1%).

DOCETAXEL

Docetaxel is a potent inhibitor of microtubule assembly and disassembly. Two clinical trials demonstrated the benefits of adding docetaxel chemotherapy to ADT for mHSPC patients.

In the phase III CHAARTED study,[99] 790 patients with mHSPC were equally randomized to receive either ADT in combination with docetaxel (75mg/m^2) for up to 6 cycles or ADT alone. In an updated reporting on the trials, at a median follow-up of 53.7 months, the median OS was 57.6 months for the chemo-hormonal therapy arm versus 47.2 months for ADT alone (HR=0.72; 95% CI: 0.59 to 0.89; p=0.0018). The median time to clinical progression was 33.0 months for the combination arm versus 19.8 months in the ADT alone arm (HR in the combination arm=0.62; 95% CI: 0.51 to 0.75; p<0.001).

Similarly, in the STAMPEDE trial, ADT plus docetaxel significantly improved median OS compared with ADT alone. The study randomly assigned 2,962 men 2:1:1:1 to receive SOC defined as hormone therapy for at least 2 years, SOC plus zoledronic acid, SOC plus docetaxel, or SOC with zoledronic acid and docetaxel. Docetaxel (75mg/m^2) was given for six 3-week cycles with prednisolone (10mg) daily. Patients were followed up 6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5 years, then annually. At a median follow-up of 43 months, median OS was 71 months for SOC compared to 81 months for SOC plus docetaxel (HR=0.78; 95% CI: 0.66 to 0.93; p=0.006). SOC plus docetaxel also improved median failure-free survival at 37 months compared 20 months with SOC alone. The durability of these results was supported in an update of this trial. At a median follow-up of 78.2 months, there were 494 deaths on SOC. There was good evidence of benefit in docetaxel over SOC on OS (HR=0.81; 95% CI: 0.69 to 0.95; p=0.009). Analysis of other outcomes found evidence of benefit for docetaxel over SOC in failure-free survival (HR=0.66; 95% CI: 0.57 to 0.76; p<0.001) and PFS (HR=0.69; 95% CI: 0.59 to 0.81; p<0.001).[97]

Since the publication of these two studies, additional trials (PEACE-1 and ARASENS) demonstrated that the addition of abiraterone or darolutamide to ADT and docetaxel improved OS.[100, 101] Therefore, doublet therapy with ADT and docetaxel alone is not advised unless patient cannot receive ARPI. Patients with high-volume disease should be considered for triplet therapy (see Guideline Statement 16).

16. In select mHSPC patients, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. (*Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B*)

The optimal patients for consideration of "dual intensification" or "triplet therapy" are best represented by the population enrolled in the following two completed trials – patients with de novo disease who are free of major comorbidities.

Two recent phase III randomized trials have demonstrated improvement in OS in patients with de novo metastatic prostate cancer receiving either abiraterone acetate (with prednisone) or darolutamide in addition to ADT and docetaxel.

The PEACE-1 trial[100] enrolled 1,173 patients with de novo metastatic prostate cancer who were randomized to receive ADT plus docetaxel (considered the SOC) plus radiotherapy, SOC plus abiraterone/prednisone or SOC plus abiraterone/prednisone and radiotherapy. In the initial analysis of the study, patients treated with SOC plus abiraterone/prednisone had an improvement in both OS (HR=0.82; 95.1% CI: 0.69 to 0.98; p=0.030) and r-PFS (HR=0.54; 99.9% CI: 0.41 to 0.71; p<0.0001) with some increase in toxicity in the abiraterone group, primarily being more hypertension.

The ARASENS phase III study[101] enrolled 1,306 patients with mHSPC (86.1% of enrolled patients had de novo metastatic disease) and randomized them to receive either darolutamide or placebo in combination with ADT and docetaxel. The trial demonstrated that the combination of darolutamide plus ADT/docetaxel resulted in improved OS, with the risk of death reduced by 32.5% (HR=0.68; 95% CI: 0.57 to 0.80; p<0.001). The frequency of grade 3/4 events was similar between the treatment arms.[102]

As the majority of patients treated in both PEACE-1 and ARASENS had de novo metastatic disease, the role of "dual intensification" or "triplet therapy" in patients with mHSPC with progression following curative-intent local therapy remains undefined.

THERAPEUTIC DECISION-MAKING IN MHSPC

Unfortunately, no comparative data on efficacy exist between the previously discussed options. The clinician should consider factors like age and comorbidities when

choosing chemotherapy, where toxicity might be more difficult for older patients than fit, younger patients. Enzalutamide, apalutamide, and darolutamide do present a small risk of seizures, so patients with a seizure disorder should be considered for a drug like abiraterone acetate plus prednisone.

In terms of intermittent ADT, SWOG 9346[103] evaluated intermittent ADT compared with continuous ADT and did not demonstrate non-inferiority in mHSPC. In fact, there was a non-significant benefit in OS with continuous ADT. Given all of the recent data suggesting that additional therapy added to continuous ADT significantly improves OS, the Panel generally advises against intermittent ADT.

17. In select mHSPC patients, clinicians may offer primary radiotherapy to the prostate in combination with ADT with or without an ARPI. (*Conditional Recommendation; Evidence Level: Grade C*)

Two recent phase III randomized trials examining ADT and prostate radiotherapy versus ADT alone in men with metastatic prostate cancer demonstrated no difference in OS. However, subgroup analyses from these trials suggested that patients with lower metastatic burden may derive greater benefit from local therapy. In STAMPEDE Arm H, a prespecified subgroup analysis using the CHAARTED definition demonstrated an OS benefit for patients with low-volume metastatic disease treated with ADT plus prostate radiotherapy.[74] Importantly, these trials were conducted largely prior to routine use of contemporary systemic therapy intensification. More recent data from the PEACE-1 trial evaluated prostate radiotherapy in the setting of intensified systemic therapy, including abiraterone with or without docetaxel, and demonstrated improved disease control endpoints and reduced serious genitourinary events with the addition of prostate radiotherapy, although no OS benefit was observed. Taken together, these data support a conditional recommendation for prostate radiotherapy in combination with ADT in select patients with mHSPC.

The HORRAD trial reported on 432 patients randomized either to ADT alone or ADT with EBRT to the prostate.[104] Median PSA was 142ng/mL, and 67% of patients had more than 5 osseous metastases by conventional imaging. OS was not different (HR=0.9; 95% CI: 0.7 to 1.14; p=0.4), but median time to PSA progression was improved in the EBRT arm (HR=0.78; 95% CI: 0.63 to 0.97; p=0.02). A hypothesis was generated that survival might be improved in a subgroup of patients with low metastatic burden (HR=0.68; 95% CI: 0.42 to 1.10). In the STAMPEDE trial, 2,061 men with metastatic HSPC were randomized to ADT alone versus ADT plus prostate radiation given at moderate doses and with unconventional fractionation (36Gy in 6 fractions over 6 weeks, or 55Gy in 20 daily fractions).[74] Radiotherapy improved failure-free survival (HR=0.76; 95% CI: 0.68 to 0.84; p<0.0001), but not OS (HR=0.92; 95% CI: 0.80 to 1.06; p=0.266) similar to HORRAD. An additional pre-specified analysis utilizing the CHAARTED definition of low-volume cancer encompassing 40% of the population was performed. Low-volume metastatic disease demonstrated a benefit to ADT plus radiation (HR=0.68; 95% CI: 0.52 to 0.90; p=0.007) with 3-year survival 73% with ADT alone versus 81% with ADT and radiotherapy. Toxicity is important to minimize in patients who will not be cured of their metastatic disease. There was no significant difference in grade ≥3 toxicity with the addition of radiotherapy (HR=1.01; 95% CI: 0.87 to 1.16; p=0.94).

More recently, the PEACE-1 trial evaluated prostate radiotherapy in the context of intensified systemic therapy for patients with de novo mHSPC using a 2×2 factorial design. Patients received ADT with or without docetaxel and were randomized to receive abiraterone, prostate radiotherapy, both, or neither. In patients with low-volume metastatic disease treated with abiraterone, the addition of prostate radiotherapy improved rPFS (HR=0.65; 99.9% CI: 0.36 to 1.19; p=0.019), whereas no rPFS benefit was observed with radiotherapy in patients not receiving abiraterone (HR=1.08; 99.9% CI: 0.65 to 1.80; p=0.61). Prostate radiotherapy did not improve OS in patients with low-volume disease (HR=0.98; 95.1% CI: 0.74 to 1.28; p=0.86) or in the overall study population. However, radiotherapy was associated with delayed progression to castration-resistant disease in patients with low-volume metastatic disease (HR=0.74; 95% CI: 0.60 to 0.92; p=0.0069) and reduced the incidence of serious genitourinary events regardless of metastatic burden, without an increase in grade ≥3 toxicity.

Physicians have suggested these results point to the benefits of local therapy raising the question whether radical prostatectomy might have the same results. These trials are ongoing, and at present the use of surgery should be considered investigational and only conducted within the context of a trial. In earlier studies such as STAMPEDE trial,[74] no patients received concurrent abiraterone acetate and only 18% received early

docetaxel, limiting conclusions regarding the integration of prostate radiotherapy with contemporary systemic therapy. More recent data from PEACE-1 demonstrate that prostate-directed radiotherapy can be safely delivered in combination with intensified systemic therapy, including abiraterone with or without docetaxel, and is associated with improved disease control and reduced serious genitourinary events, although no OS benefit has been demonstrated.

18. **Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (*Strong Recommendation; Evidence Level: Grade A*)**

With compelling level A evidence supporting the use of abiraterone acetate plus prednisone, apalutamide, enzalutamide or darolutamide in combination with ADT in men with newly diagnosed mHSPC, the Panel believes that long-term use of first generation antiandrogens bicalutamide, flutamide, nilutamide in lieu of the above noted agents cannot be supported.

In the first week after LHRH agonists are administered, there is typically a surge in luteinizing hormone resulting in an increase in circulating testosterone. This may cause clinical “flares,” which may be associated with worsening of disease symptoms (e.g., bone pain, urinary tract obstruction) in approximately 10% of patients. This surge can be “blocked” by short term (e.g., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[105]

19. **In mHSPC patients with HRR gene alterations, particularly BRCA 2, clinicians may offer the combination of ADT, abiraterone, and niraparib. *(Expert Opinion)***

Recent phase III evidence suggests a potential role for PARP inhibition in select patients with mHSPC harboring HRR gene alterations, particularly BRCA2. The AMPLITUDE trial[106] was a randomized, double-blind, phase III study that enrolled 696 patients with newly diagnosed mHSPC and predefined HRR alterations, randomized to receive niraparib plus abiraterone versus placebo plus abiraterone, all in combination with ADT. In the overall HRR-altered population, the addition of niraparib significantly improved rPFS, with a 37% reduction in the risk of radiographic progression or death compared with abiraterone alone (HR=0.63; 95% CI: 0.49 to 0.80; p=0.0001). The magnitude of benefit was greatest among patients with BRCA1 or BRCA2 alterations, who comprised approximately 55% of the study population. In this subgroup, niraparib plus abiraterone was associated with a 48% reduction in the risk of radiographic progression (HR=0.52; 95% CI: 0.37 to 0.72; p<0.0001), largely driven by the BRCA2 subset. By contrast, benefit among patients with non-BRCA HRR alterations was uncertain and should be interpreted with caution. In an exploratory analysis of patients without BRCA1/2 alterations, the hazard ratio for rPFS) was 0.81 (95% CI: 0.56 to 1.18). These data do not support routine extrapolation of benefit to non-BRCA HRR-altered patients.

OS data from AMPLITUDE remains immature. While secondary endpoints, including time to symptomatic progression, favored the niraparib combination, longer follow-up is required to determine the impact on OS. Treatment with niraparib was associated with higher rates of adverse events, including higher rates of treatment discontinuation due to adverse events (14.7% versus 10.3%) and grade 3/4 toxicity (75.2% versus 58.9%), highlighting the importance of careful patient selection and toxicity monitoring. These findings represent the first phase III evidence evaluating PARP inhibitor use in the frontline metastatic hormone-sensitive setting and provide a rationale for incorporating PARP inhibition into treatment discussions for BRCA-positive patients.

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

20. **In nmCRPC patients, clinicians should obtain serial PSA measurements at three- to six-month intervals and calculate a PSADT starting at the time of development of castration-resistance. (*Clinical Principle*)**

Monitoring of men with nmCRPC should include serial measurements of PSA, whether patients are receiving ADT alone or ADT with an additional AR directed therapy (apalutamide, darolutamide, enzalutamide). This allows clinicians to monitor disease status and should be performed every three- to six-months. PSADT should be calculated for men with a rising PSA in the setting of ongoing ADT (castration-resistance) as PSADT is useful

in determining which men are at highest risk of developing metastatic lesions or dying from prostate cancer.[107] PSADT <10 months was used to identify the highest risk population for inclusion in the three trials that led to approval of the AR antagonists for men with nmCRPC and is recommended to consider when adding one of the medications to ADT in men with nmCRPC.[15-17] However, FDA approval of these agents does not specify a doubling time.

21. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional or PSMA PET imaging at intervals of 6 to 12 months. (*Expert Opinion*)

In addition to monitoring PSA, routine use of conventional or PSMA PET imaging should be integrated into monitoring the disease status of men with nmCRPC. The suggested interval of imaging is 6 to 12 months, with the exact interval determined by the PSADT calculation, the development of symptoms, and patient/physician preference. A PSADT of ≤10 months is associated with a high risk of developing metastatic disease or dying from prostate cancer.[108] Continued monitoring with routine imaging is recommended for patients on ADT alone and patients on ADT plus an AR antagonist (apalutamide, darolutamide, enzalutamide). In patients with mCRPC treated with enzalutamide prior to chemotherapy in the PREVAIL trial, radiographic progression occurred in 24.5% of patients without PSA progression, suggesting that routine imaging can identify a significant portion of patients with radiographic progression who would otherwise not be identified.[108] The Panel extrapolates this principle to the nmCRPC population, particularly for men on additional AR antagonist treatment.

Once a patient has started ART therapy for nmCRPC as noted below, the imaging intervals can be extended to annually in the absence of other indicators of progression.

Treatment

22. Clinicians should offer apalutamide, darolutamide, or enzalutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (*Strong Recommendation; Evidence Level: Grade A*)

In the past clinicians used bicalutamide in the nmCRPC patient population as a method to reduce PSA in the absence of trials demonstrating a clinical benefit. In 2018, apalutamide became the first FDA-approved treatment for patients with non-metastatic disease; shortly thereafter, enzalutamide and darolutamide were also approved in this patient population. There are now three FDA approved agents that demonstrate superiority in terms of prolonging MFS by nearly two years. Bicalutamide is no longer a viable strategy for treatment of this patient population. It should also be noted that there are no head-to-head clinical trials demonstrating superiority of any one of these agents (apalutamide, darolutamide, enzalutamide) over the other two.

APALUTAMIDE

In the double-blind, placebo-controlled, phase III SPARTAN trial, Smith et al. randomly assigned 1,207 men in a 2:1 ratio to receive apalutamide (240mg per day) or placebo.[16] All patients had a diagnosis of nmCRPC with a PSADT ≤10 months and continued on ADT. At the time of planned primary analysis, median MFS was 40.5 months in the apalutamide group compared to 16.2 months in the placebo group (HR=0.28; 95% CI: 0.23 to 0.35; p<0.001), representing a 72% reduction in the risk of distant metastasis or death. Median OS was not reached in the apalutamide group versus 39.0 months in the placebo group (HR=0.70; 95% CI: 0.47 to 1.04; p=0.07). Secondary endpoints including time to symptomatic progression (HR=0.45; 95% CI: 0.32 to 0.63; p<0.001) and time to metastasis (HR=0.27; 95% CI: 0.22 to 0.34, p<0.001) were significantly longer in the apalutamide arm compared to placebo. Median PFS was 40.5 months in the apalutamide group versus 14.7 months in the placebo group (HR=0.29; 95% CI: 0.24 to 0.36; p<0.001). Overall, 10.6% of patients receiving apalutamide discontinued treatment due to adverse events compared to 7.0% of patients receiving placebo. The adverse events that occurred in ≥15% of patients in either group (apalutamide versus placebo) included fatigue, hypertension, rash, diarrhea, nausea, weight loss, arthralgia, and falls.

DAROLUTAMIDE

ARAMIS is a randomized, double-blind, placebo-controlled, phase III study assessing the safety and efficacy of darolutamide in men with nmCRPC.[17] All patients had nmCRPC with a PSADT ≤10 months and PSA ≥2ng/mL (median 9.0 and 9.7ng/mL in the darolutamide versus placebo arms, respectively). The study enrolled 1,509 patients who were randomized in a 2:1 fashion to ADT with darolutamide or ADT with placebo, with a primary endpoint of MFS survival. The

median MFS was 22 months longer with darolutamide compared to placebo (40.4 months with darolutamide versus 18.4 months with placebo, HR=0.41; 95% CI: 0.34 to 0.50; p<0.001). Median OS was not reached in either group, but there was a lower risk of death with darolutamide than placebo (HR=0.71; 95% CI: 0.50 to 0.99; p=0.045). The median time to PSA progression was 33.2 months versus 7.3 months in the darolutamide versus placebo groups, respectively (HR=0.13; 95% CI: 0.11 to 0.16; p<0.001). Treatment discontinuation due to adverse events occurred in 8.9% of patients receiving darolutamide compared to 8.7% receiving placebo.

ENZALUTAMIDE

PROSPER is a randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and tolerability of enzalutamide in nmCRPC patients.[15] All patients had nmCRPC with a PSADT ≤10 months. The 1,401 patients were randomized (2:1) to enzalutamide 160mg per day or placebo. Both arms continued ADT. During the first interim analysis of OS, 103 patients (11%) in the enzalutamide group and 62 (13%) in the placebo group had died. Median OS was not reached in either group. As of June 2017, a total of 219 patients (23%) in the enzalutamide group had metastases or had died, as compared with 228 (49%) in the placebo group. Median MFS was approximately 22 months longer in the enzalutamide arm at 36.6 months compared to 14.7 months in the placebo group (HR=0.29; 95% CI: 0.24 to 0.35; p<0.001). Additionally, median time to PSA progression was approximately 33 months longer in patients receiving enzalutamide compared to those receiving placebo (37.2 months in the enzalutamide group compared to 3.9 months in the placebo group; HR=0.07; p<0.001). Following completion of the systematic review for this guideline, additional data were released on OS as of October 2019. In the enzalutamide group, the median OS was 67.0 months (95% CI: 64.0 to not reached) and 56.3 months (95% CI: 54.4 to 63.0) in the placebo group. Treatment with enzalutamide plus ADT was associated with a 27% lower risk of death versus placebo plus ADT (HR=0.73; 95% CI: 0.61 to 0.89; p=0.001).[109] Adverse events as the primary reason for treatment discontinuation occurred in 87 patients (9%) receiving enzalutamide compared to 28 (6%) receiving placebo. Deaths due to adverse events on trial irrespective of attribution occurred in 32 patients (3%) receiving enzalutamide and 3 patients (1%) receiving placebo. Adverse events noted to occur more frequently with enzalutamide included convulsion, hypertension, neutropenia, memory impairment disorders, and major cardiovascular events.

Data from the STRIVE and TERRAIN trials[110, 111] suggest that bicalutamide is not a reasonable option for treatment of men with nmCRPC. In STRIVE, Penson et al. randomized (1:1) a mixed population of men diagnosed with non-metastatic (n=139) or metastatic (n=257) CRPC to receive enzalutamide 160mg per day or bicalutamide 50mg per day. Both arms remained on ADT. The treatment effect of enzalutamide on PFS was consistently favorable across all patient populations, and median PFS was not reached with enzalutamide in the non-metastatic population compared with 8.6 months with bicalutamide (HR=0.24; 95% CI: 0.14 to 0.42; p<0.001). PSA decline, defined as ≥50% and ≥90% decline from baseline, favored enzalutamide (enzalutamide: 91% versus bicalutamide: 42% and enzalutamide: 76% versus bicalutamide: 12%, respectively). Analysis of other secondary endpoints, such as decreased risk of radiographic progression or death, favored enzalutamide with a 76% risk reduction (HR=0.24; 95% CI: 0.10 to 0.56). In TERRAIN, men with mCRPC were randomized to treatment with ADT plus enzalutamide 160mg per day or bicalutamide 50mg per day, and were followed to assess the primary endpoint of PFS. Median PFS was significantly prolonged in men treated with enzalutamide when compared with bicalutamide (15.7 months versus 5.8 months for enzalutamide versus bicalutamide, respectively, HR=0.44; 95% CI: 0.34 to 0.57; p<0.0001).[111]

The Panel does not recommend the use of abiraterone acetate plus prednisone for men with nmCRPC because of other options and lack of an FDA-approved indication for this clinical space. However, in a single arm study of 131 men with nmCRPC at high risk of developing metastatic disease as identified by a PSADT of ≤10 months, patients treated with abiraterone acetate plus prednisone had a PSA significantly reduced by ≥ 50% in 86.9% of cases (p<0.0001).[112] Additionally, median time to PSA progression was 28.7 months (95% CI: 21.2 to 38.2). The data are not considered sufficient to confirm clinical benefit in the nmCRPC population, particularly in the setting of three FDA-approved alternative treatment options.

23. Clinicians may recommend observation with continued ADT to nmCRPC patients, particularly those at lower risk (PSADT >10 months) for developing metastatic disease. (*Clinical Principle*)

It is the Panel's judgment that observation with continued ADT is recommended for patients with a PSADT >10 months. These patients have a lower risk of developing metastatic disease than patients with a PSADT ≤10 months.[113] This statement is based on clinical principle rather than evidence as patients with a PSADT >10 months were not included in the clinical trials that led to the approval of apalutamide, darolutamide, or enzalutamide for nmCRPC; and the precise benefit/risk ratio for a given patient should be determined by the treating clinician.

24. Clinicians should not offer systemic chemotherapy or immunotherapy to nmCRPC patients outside the context of a clinical trial. (*Clinical Principle*)

The Panel strongly recommends against the use of chemotherapy, immunotherapy, or other agents not FDA approved for use in the nmCRPC setting. There is a lack of evidence suggesting benefit, and these agents, like any medication, have associated toxicity. The combination of no known benefit with known and potentially serious harms supports the decision to recommend against use of these agents in men with nmCRPC.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

25. In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (lymph node, bone, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision-making. (*Clinical Principle*)

There are established laboratory and imaging characteristics known to be associated with prognosis among men with mCRPC. As such, it is recommended that a baseline laboratory and imaging assessment be performed to inform discussions around prognosis and clinical decision-making. Known laboratory risk-factors associated with increasing risk of mortality include elevated LDH, testosterone <20 to 50ng/dL, higher PSA, and shorter PSADT.[9, 36, 37, 114, 115] There are established imaging findings also known to be associated with increasing risk of mortality.[116] Increasing burden of metastatic disease in the form of the number of metastatic sites is associated with increasing risk of overall mortality. Additionally, there are known relationships between location of metastases and risk of mortality.[117] Specifically, visceral metastases are known to portend the highest risk of mortality (HR=1.76; 95% CI: 1.34 to 2.32 versus lymph node) followed by bone metastases (HR=1.52; 95% CI: 1.20 to 1.93 versus lymph node).[118]

In addition to laboratory and imaging parameters, performance status and the extent of disease-related symptoms are strongly associated with mortality. Numerous studies have characterized the inverse relationship between performance status and risk of mortality.[36, 116, 119] Independently, prostate cancer-related pain is known to be strongly associated with the risk of mortality.[38] Men with mCRPC represent a heterogeneous group with a wide distribution of disease-related symptoms. Given the known relationships between disease-related symptoms and prognosis, it is incumbent upon the treating clinician to perform a thorough symptom inventory at the time of assessment to ensure adequate symptom management and to incorporate the individual patient's symptom burden into discussions around prognosis and treatment selection.

26. In mCRPC patients without PSA progression or new symptoms, clinicians should perform imaging at least annually. (*Expert Opinion*)

Response to treatment and/or disease progression among men with mCRPC may be evaluated through PSA testing, imaging, or change in disease-related symptoms. It is recommended that men with mCRPC undergo imaging at least annually owing to the fact that, in patients with mCRPC treated with enzalutamide prior to chemotherapy in the PREVAIL trial, radiographic progression occurred in 24.5% of patients without PSA progression. This suggests that routine imaging can identify a significant portion of patients with radiographic progression who would otherwise not be identified.[108] The precise timing of imaging among men with mCRPC should be determined by multiple factors including biochemical response to treatment, change in disease-related symptoms, and patient preference. Furthermore,

clinicians should consider known differences in biochemical response to treatment among different therapies for mCRPC when determining the interval between imaging studies.

Treatment

27. For most patients progressing to mCRPC who have not received prior ARPIs, clinicians should offer continued ADT with abiraterone acetate plus prednisone or enzalutamide. (*Strong Recommendation; Evidence Level: Grade A)*

Abiraterone acetate plus prednisone and enzalutamide both have an FDA indication for use in men with mCRPC. For each agent, there is randomized trial data showing a survival benefit for men with mCRPC.

ABIRATERONE ACETATE

In the placebo-controlled, double-blind, phase III COU-AA-302 study, Ryan et al.[120] randomized 1,088 men with mCRPC who had not received prior chemotherapy to receive either abiraterone acetate 1,000mg daily plus prednisone 5mg twice a day or placebo plus prednisone 5mg twice daily. The primary outcomes of the study were rPFS and OS. Participants randomized to receive abiraterone acetate plus prednisone had statistically significant improvement in rPFS (HR=0.53; p<0.001), as previously reported during interim analyses.[121] The final analysis of OS showed a statistically significant increase in patients treated with abiraterone acetate plus prednisone (HR=0.81; 95% CI: 0.70 to 0.93; p=0.0033).[120] The most common grades 3 to 4 adverse events were cardiac disorders (8% in the abiraterone acetate group versus 4% in the placebo group), increased alanine aminotransferase (6% versus <1%), and hypertension (5% versus 3%).

In the COU-AA-301 trial, de Bono et al. randomly assigned 1,195 patients who had previously received docetaxel in a 2:1 ratio to receive 5mg of prednisone twice daily with either 1,000mg abiraterone acetate or placebo. The primary endpoint was OS. After a median follow-up of 12.8 months, OS was 14.8 months in the abiraterone acetate group compared to 10.9 months in the placebo group (HR=0.65; 95% CI: 0.54 to 0.77; p<0.001). All secondary endpoints, including time to PSA progression, PFS, and PSA response rate favored the abiraterone acetate group.

ENZALUTAMIDE

In the double-blind, phase III PREVAIL study, Beer et al. randomized 1,717 chemotherapy-naïve patients to receive either enzalutamide (at a dose of 160mg) or placebo once daily.[122] Co-primary endpoints were rPFS and OS. The results showed that enzalutamide significantly decreased the risk of radiographic progression (HR=0.19; 95% CI: 0.15 to 0.23; p<0.001) and death (29% reduction in the risk of death; HR=0.71; 95% CI: 0.60 to 0.84; p<0.001). Enzalutamide also showed a benefit with respect to all secondary endpoints, including the time until the initiation of chemotherapy (HR=0.35; 95% CI: 0.30 to 0.40; p<0.001) in a group of men with mCRPC and a median follow-up duration for survival of approximately 22 months. Adverse events that occurred in 20% or more of patients receiving enzalutamide at a rate that was at least 2 percentage points higher than that in the placebo group were fatigue, back pain, constipation, and arthralgia.

In the phase III, double blind AFFIRM study, Scher et al. stratified 1,199 men with CRPC after chemotherapy in a 2:1 ratio to receive enzalutamide (160mg per day) or placebo. The primary endpoint was OS. At the time of planned interim analysis, the median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR for death in the enzalutamide group=0.63; 95% CI: 0.53 to 0.75; p<0.001). Enzalutamide was superior over placebo with respect to all secondary endpoints, including PSA reduction by 50% or more, soft-tissue response rate, QOL response rate, time to PSA progression, rPFS, and the time to first SRE.

More recently, enzalutamide was evaluated in combination with radium-223 in men with bone metastases who were ARPI naive in the PEACE-3 trial.[123] Results showed a statistically significant rPFS and OS benefit of 7.3 months for the combination at the interim analysis when used in first line mCRPC. This was associated with 31% decreased risk of death (HR=0.69). The OS was re-iterated at the final OS analysis. This study also re-emphasized the importance of bone protective agents which were ultimately mandated in a study amendment given the high fracture rates seen in both arms.

28. In mCRPC patients with disease progression following treatment with an ARPI, clinicians should offer docetaxel. (*Strong Recommendation; Evidence Level: Grade B*)

Docetaxel (typically in combination with 10 mg prednisone/day) is an effective option in both mCRPC and mHSPC and should be considered as standard first-line chemotherapy in the setting of mCRPC based on a randomized, multicenter, active-controlled trial (TAX 327),[22] which demonstrated a statistically significant OS advantage over mitoxantrone, with a median survival of 18.9 months versus 16.5 months (HR=0.761; 95% CI: 0.619 to 0.936). The palliative data from this study is compelling demonstrating significant pain reduction and improvement in QOL.[124]

29. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (*Conditional Recommendation; Evidence Level: Grade B*)

Sipuleucel-T is an immunotherapy for the management of mCRPC. Sipuleucel-T immunotherapy is an FDA-approved agent in this setting based upon the results of the IMPACT trial,[25] published in 2010. In this randomized double-blind placebo controlled clinical trial, 512 men with asymptomatic or minimally-symptomatic mCRPC and good functional status were randomized to receive either sipuleucel-T or placebo on a 2:1 basis. Compared to placebo, sipuleucel-T was associated with a relative reduction of 22% in the risk of death (HR=0.78; 95% CI: 0.61 to 0.98 p=0.03). Median survival in the sipuleucel-T arm was 25.8 months compared to 21.7 months in the placebo arm. It is worth noting that patients receiving sipuleucel-T therapy rarely (<10%) exhibit a clinical, serologic or radiographic response, and, as such, should be counseled appropriately not to expect to see a decline in PSA or reduction in radiologic volume of disease when undergoing this treatment. Enrollment was restricted to patients with ECOG performance status scores of 0 or 1 who were asymptomatic or minimally symptomatic; patients with visceral metastases were excluded. As such, sipuleucel-T should only be considered for patients with asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T is not associated with objective anti-tumor activity; its use is not appropriate for patients with large tumor burdens, those with visceral disease or with rapidly progressive disease. The use of sipuleucel-T immunotherapy is not recommended in symptomatic disease that necessitates opioid use, consistent with the FDA indication for this approach.

30. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm. (*Strong Recommendation; Evidence Level: Grade B*)

Radium-223 is an α-emitting radiopharmaceutical capable of inducing double strand DNA breaks in cancer cells while minimizing exposure to surrounding marrow. The use of radium-223 for the treatment of bone metastases relies on the chemical similarity to calcium and the ability of the α-radiation and the short-lived decay products of radium-223 to kill cancer cells. The short range of α-radiation reduces the damage to surrounding healthy tissue creating a more localized effect compared to other radionuclide therapies, such as strontium-89. This is an appropriate treatment for patients with symptomatic bone pain and non-visceral metastases.

A phase III trial[26] with radium-223 in symptomatic men with progressive mCRPC with or without prior docetaxel exposure and no evidence of visceral metastasis reported improvement in median survival; 14.9 months versus 11.3 months (HR=0.70; 95% CI: 0.58 to 0.83; p<0.001) in favor of radium-223 over placebo. Time to first skeletal-related event (SRE) improved from 9.8 month with placebo to 15.6 months with radium-223 (HR=0.66; 95% CI: 0.52 to 0.83; p<0.001). Significant improvements in QOL measurements were reported in the patients treated with radium-223. Of the 921 patients of this trial, those receiving treatment were given 6 intravenous injections with a dose of 50 kBq per kilogram of body weight every 4 weeks. Rates of grade 3 or 4 neutropenia and thrombocytopenia were low at 2.2% and 6.3%, respectively.[26]

As radium-223 targets bone only and is not associated with a PSA decline in a majority of patients, it is imperative for the clinician to carefully assess the patient on a monthly basis. Progression in non-bone sites is not infrequent during this six-month period of treatment. Given the lack of utility of PSA measurement in this space, the Panel recommends obtaining abdomen/pelvis CT imaging and chest x-ray even in the absence of symptoms prior to cycle four (of planned six monthly cycles) to assess for occult disease progression.

Clinicians should also be advised against concurrent use of abiraterone acetate plus prednisone in combination with radium-223 given the association with a higher risk of skeletal related events.[125]

31. In mCRPC patients with disease progression following treatment with an ARPI (with or without prior docetaxel), and a positive PSMA PET/CT, clinicians should offer ^{177}Lu-PSMA-617. (*Strong Recommendation; Evidence Level Grade: B*)

In the phase III VISION trial, patients with progressive mCRPC and PSMA PET avid disease following therapy with an ARPI and docetaxel treated with ^{177}Lu-PSMA-617 plus SOC had improved PFS and OS compared to patients receiving SOC alone at a median follow-up of approximately 21 months.[126] This study led to the approval of ^{177}Lu-PSMA-617 for progressive mCRPC in 2022.

More recently, ^{177}Lu-PSMA-617 was evaluated in the chemotherapy-naïve mCRPC setting. The phase III multi-national PSMAfore trial[127] randomized patients who had progressed on prior ARPI to ^{177}Lu-PSMA-617 or change of ARPI and evaluated time from randomization to radiographic progression or death. Results indicated a median rPFS of 9.3 months versus 5.55 months in the ^{177}Lu-PSMA-617 versus ARPI change group, respectively. Importantly, there was a favorable safety profile with a low incidence of high-grade adverse events in the treatment arm.

32. In mCRPC patients who received prior docetaxel chemotherapy either in the mHSPC or mCRPC setting, clinicians may offer cabazitaxel. (*Conditional Recommendation; Evidence Level: Grade B*)

Three cytotoxic chemotherapy regimens have been approved by the FDA for treatment of mCRPC: mitoxantrone, docetaxel, and cabazitaxel. Mitoxantrone was not associated with a survival benefit and is generally not recommended for most patients with mCRPC. Cabazitaxel was approved as second line chemotherapy in 2010 based on the results of the TROPIC trial.[24] TROPIC randomized 755 men with mCRPC who had previously received docetaxel chemotherapy and demonstrated median survival of 15.1 months (95% CI: 14.1 to 16.3) in the cabazitaxel group and 12.7 months (11.6 to 13.7) in the mitoxantrone group. The HR for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0.70 (95% CI: 0.59 to 0.83, p<0.0001). There was a clear OS benefit to cabazitaxel chemotherapy after docetaxel.

The FIRSTANA trial was a phase III randomized trial that failed to demonstrate superiority of cabazitaxel over docetaxel as first-line chemotherapy for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer.[128]

33. In mCRPC patients who received prior docetaxel chemotherapy and an ARPI, clinicians should recommend cabazitaxel rather than an alternative ARPI. (*Strong Recommendation; Evidence Level: Grade B*)

Optimal third line therapy for mCRPC is unknown. The majority of patients will receive one ART targeted therapy with abiraterone acetate plus prednisone or enzalutamide and docetaxel chemotherapy. The CARD trial[129] tested the efficacy and safety of cabazitaxel versus the alternative ART therapy in patients with mCRPC who progressed after two prior therapies. The primary end point was imaging-based PFS. Secondary end points included survival, response, and safety. A total of 255 patients were randomized, and progression or death was reported in 73.6% in the cabazitaxel group compared with 80.2% in the group that received a second ART (HR=0.54; 95% CI: 0.40 to 0.73; p<0.001). The median OS was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling-targeted inhibitor (HR for death=0.64; 95% CI: 0.46 to 0.89; p=0.008). The median PFS was 4.4 months with cabazitaxel and 2.7 months with an androgen-signaling-targeted inhibitor (HR for progression or death=0.52; 95% CI: 0.40 to 0.68; p<0.001). A PSA response occurred in 35.7% and 13.5% of the patients, respectively (p<0.001), and tumor response was noted in 36.5% and 11.5% (p=0.004). Adverse events of grade 3 or higher occurred in 56.3% of patients receiving cabazitaxel and in 52.4% of those receiving an androgen-signaling-targeted inhibitor.

It is important to note that the CARD study enrolled an enriched group of patients with advanced mCRPC, with more than two thirds having disease-related pain. There may be clinical settings as in long-term response to the initial agent (abiraterone acetate/enzalutamide) or asymptomatic patients with disease progression in whom a therapeutic trial of the alternative agent is reasonable.

Cabazitaxel significantly improved a number of clinical outcomes, as compared with an additional ART (abiraterone acetate or enzalutamide), in patients with mCRPC who had been previously treated with docetaxel and the alternative androgen-signaling-targeted agent (abiraterone acetate or enzalutamide). The magnitude of this benefit, improvement in multiple secondary endpoints, and other evidence demonstrating that sequencing serial ART therapies has limited efficacy suggests that cabazitaxel chemotherapy remains an important option for mCRPC patients in the third line.

34. Clinicians may offer a PARP inhibitor to select patients with deleterious germline or somatic HRR gene-mutated mCRPC who have progressed on prior ARPIs. Platinum-based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (*Conditional Recommendation; Evidence Level: Grade C*)

PARP inhibitors leverage defects in DNA repair to provide improved outcomes in men with advanced prostate cancer who have mutations in DNA repair enzymes central to homologous recombination DNA repair. Defects in DNA repair occur in up to 30% of men with mCRPC, and such cancer cells depend instead on PARP-regulated DNA repair.[130] Therefore, inhibition of PARP in these tumors results in cell death.[131]

In the randomized, open-label, phase III PROfound trial, de Bono et al. randomly assigned 387 patients with progression on enzalutamide or abiraterone acetate in a 2:1 ratio to receive olaparib (300mg twice daily) or the physician's choice of enzalutamide or abiraterone acetate (control).[43] Nineteen percent of patients randomized to antiandrogen therapy had previously received both enzalutamide and abiraterone acetate; the trial did not report the proportion of patients among the remaining 81% who received the alternative antiandrogen or report results in this subgroup. All patients had a qualifying alteration in pre-specified genes with a direct or indirect role in homologous recombination repair. Cohort A had at least 1 alteration in BRCA1, BRCA2, or ATM; and cohort B had alterations in any of the 12 other pre-specified genes (BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L). The primary endpoint was imaging-based PFS in cohort A. Median PFS was 7.4 months in the olaparib group versus 3.6 months in the control group (HR for progression or death=0.34; 95% CI: 0.25 to 0.47; p<0.001). Median OS in cohort A was 18.5 months with olaparib compared to 15.1 months in the control group. Investigators noted that anemia and nausea were the main toxic effects seen in patients on olaparib.

In addition to olaparib, rucaparib is also FDA-approved for patients with deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy. The Triton 3 study demonstrated that rucaparib significantly improved rPFS compared to physician's choice of docetaxel or a second-generation ARPI in patients with BRCA-mutated metastatic castration-resistant prostate cancer.[132]

Platinum-based chemotherapy also has a mechanism of action that correlates with defects in homologous recombination DNA repair. Preliminary data have demonstrated that, similar to PARP inhibition, carboplatin may improve outcomes in men with similar DNA defects.[133] However, to date there are no randomized data supporting its use. In a retrospective analysis of a single-institution cohort of men with mCRPC, pathogenic germline BRCA2 variants were noted in 8 of 141 participants. Six of eight (75%) of those men experience PSA decline >50% within 12 weeks compared to 23 of 133 (17%) of non-carriers (absolute difference=58%; 95% CI: 27% to 88%; p<0.001).[133]

35. Clinicians may offer a PARP inhibitor in combination with an ARPI to select patients with deleterious germline or somatic HRR gene-mutated mCRPC. (*Conditional Recommendation; Evidence Level: Grade C*)

More recently, PARP-inhibitors in combination with abiraterone or enzalutamide were FDA approved in patients with mCPRC with specific DDR mutations on the basis of three randomized trials.

PROpel[134, 135] randomized mCRPC patients who were unselected for DDR status to receive olaparib plus abiraterone/prednisone versus placebo plus abiraterone/prednisone. The trial met its primary endpoint with a median rPFS of 24.8 versus 16.6 months (HR=0.66; 95% CI: 0.54 to 0.81; p<0.001). However, the trial failed to demonstrate OS benefit. The FDA approved the combination only for BRCA-mutated mCRPC, determining that the modest benefit in non-BRCA patients did not justify the added toxicity.

Magnitude was a biomarker-selected phase III trial enrolling patients into DDR positive and DDR negative cohorts comparing niraparib + abiraterone/prednisone versus placebo plus abiraterone/prednisone.[136-138] Futility analysis led to the closure of the DDR-negative cohort. There was a statistical improvement in median rPFS in the DDR + cohort, however the FDA determined this benefit was driven by the BRCA subgroup with FDA approval of niraparib/abiraterone in BRCA mutated mCPRC only patients.

TALAPRO 2[139-142] enrolled mCRPC patients into an DDR unselected cohort and a DDR-deficient cohort comparing talazoparib + enzalutamide versus placebo plus enzalutamide. In the unselected cohort median rPFS was 33.1 versus 19.5 months (HR 0.67; p<0.0001), and at final analysis (median follow-up 52.5 months), OS was statistically significant at 45.8 versus 37.0 months (HR=0.80; 95% CI: 0.66 to 0.96; p=0.016). In the DDR defecient cohort the OS benefit was 45.1 versus 31.1 months (HR=0.62; 95% CI: 0.48 to 0.81; p=0.0005). The FDA approved talazoparib/enzalutamide for DDR gene mutated mCRPC.

It is important to note that the vast majority of patients enrolled in PROpel, MAGNITUDE and TALAPRO 2 had not received prior APRI therapy prior to study enrollment and thus the efficacy of combination approaches in patients with mCRPC progression on an ARPI is unknown. Additionally, there is more therapy related toxicity and cost associated with combination therapy.

Treatment decision making in the mCRPC setting is increasingly complex and requires careful consideration of patient's treatment history, genetic test results, comorbid status, and patient preference.

36. In patients with MMR deficient or MSI-H mCRPC, clinicians should offer pembrolizumab. (*Moderate Recommendation; Evidence Level: Grade C*)

Unlike the other major urologic neoplasms such as renal cell and urothelial cancers where next generation immunotherapy agents (check point inhibitors and anti-CTLA-4 agents) have demonstrated meaningful activity, there has been limited evidence of the utility of these therapies in mCRPC.

The MMR system is a post-replicative, single-strand repair mechanism that recognizes and reverses DNA base mismatches and insertions/deletions. Compromised MMR results in MSI and a hypermutator phenotype that has been associated with chemotherapy resistance but immunotherapy sensitivity.[143]

In a case series of 1,033 patients with advanced prostate cancer 3.1% had an MSI-H/dMMR prostate cancer, with more than half of those treated with anti PD-1 therapy responding to treatment having a >50% decline in PSA.[144]

Until recently assessment of MSI status was a tissue-based assay and is still optimally done with archival or fresh tissue. Recent evidence suggests that cell-free DNA sequencing methods may allow MSI status to be determined with liquid biopsies.

In May 2017, the FDA approved pembrolizumab for patients with any metastatic MSI-H or dMMR histology that have progressed following prior treatment, and who have no satisfactory alternative treatment options.[41]

BONE HEALTH

Several factors conspire to place the average patient with metastatic prostate cancer at a higher risk of bone complications. First, the median age of onset of the disease is in the late 60s, meaning that the average patient with metastatic disease may be in his 70s (or beyond), clearly a population at risk of physiologic, age-related decreases in bone mineral density. Secondly, a primary therapeutic intervention in patients with recurrent disease (e.g., ADT) is associated with progressive loss of bone mineral density, not infrequently to the point of measurable osteopenia or frank osteoporosis, increasing the patient's fracture risk, even in patients with non-metastatic disease.[145, 146] Finally, in patients with advanced disease, bones are the most common site of metastatic disease, with many patients at some point in their course demonstrating evidence of disease in this site.

37. Clinicians should discuss the risk of osteoporosis associated with ADT and should assess the risk of fragility fracture in patients with advanced prostate cancer. (*Clinical Principle*)

Individuals with metastatic prostate cancer are at a high risk of bone complications due to age-related and treatment related loss in bone mineral density.[145-147] The Fracture Risk Assessment Tool (https://www.sheffield.ac.uk/FRAX/) is a validated resource to help predict a patient's ten-year probability of hip fracture and the ten-year probability of a major osteoporotic-related fracture (e.g., spine, forearm, hip or

shoulder fracture). This tool can be used with or without measurement of bone mineral density.

Baseline bone mineral density measurement with dual x-ray absorptiometry (DXA) may be considered in men receiving androgen deprivation and other systemic treatments for prostate cancer.[148, 149] Several observational studies have assessed changes in bone mineral density.[150-154] Many of these studies reveal that the largest decrease in bone mineral density occurs within the first year of therapy, although bone loss has been observed beyond one year of therapy. Based on these observational studies, it would be reasonable to re-assess osteoporotic-related risk (FRAX® and DXA) one-year after initiating systemic treatment, and at longer intervals thereafter.

38. Clinicians should recommend preventive treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to advanced prostate cancer patients on ADT. (*Clinical Principle*)

For patients with advanced prostate cancer, there is insufficient evidence to inform the optimal strategies for the prevention of bone loss and frailty fractures. However, for most patients, it is reasonable to inform patients about the tenets of bone health based on bone physiology, expert opinion, and syntheses of available clinical evidence.[155]

The U.S. National Osteoporosis Foundation provides easy to use recommendations for bone health maintenance (https://www.nof.org/preventing-fractures/prevention/). Recommendations include weight bearing exercises, muscle building exercises, balance exercises, smoking cessation, reduction of alcohol intake, and adequate intake of calcium and vitamin D.[155] The estimated daily calcium requirement is 1,000 to 1,200mg from food and supplements. The estimated daily vitamin D requirement is 1,000 IU from food, supplements, and sunlight. [155]

39. In advanced prostate cancer patients at high fracture risk due to bone loss, clinicians should recommend preventive treatments with bisphosphonates or denosumab and referral to physicians who have familiarity with the management of osteoporosis when appropriate. (*Clinical Principle*)

Pharmacologic strategies for osteoporosis prevention and treatment include oral bisphosphonates (e.g., alendronate, pamidronate), intravenous bisphosphonates (e.g., zoledronic acid), and subcutaneous RANK ligand inhibitors (e.g., denosumab). It is important to note that the recommended dose and treatment schedules for zoledronic acid and denosumab are different for the indications of osteoporotic fracture prevention and SRE prevention. For example, zoledronic acid is usually administered yearly for osteoporosis-related fracture prevention compared to monthly or every three months for metastatic cancer SRE prevention. Similarly, denosumab has been administered as 60mg every 6 months for osteoporosis compared to 120mg monthly for SRE prevention.

A meta-analysis[156] included 15 trials of 2,634 men with prostate cancer receiving ADT (with or without bone metastases) randomized to receive a bisphosphonate versus placebo. A meta-analysis[156] included 15 trials of 2,634 men with prostate cancer receiving ADT (with or without bone metastases) randomized to receive a bisphosphonate versus placebo. Men receiving bisphosphonates had significantly reduced risk of osteoporosis (RR=0.39; 95% CI: 0.28 to 0.55; number needed to treat [NNT] to prevent one additional patient with osteoporosis: 2.82). Osteoporosis-related fractures were also reduced among patients treated with bisphosphonates (RR=0.80; 95% CI: 0.69 to 0.94; NNT to prevent one additional fracture: 167). Amongst bisphosphonates, the greatest reduction in fractures was observed for zoledronic acid (NNT: 14.9).

Denosumab increases bone mineral density in prostate cancer patients and reduces fracture risk as well. In a trial of 1,468 men receiving ADT for prostate cancer,[157] patients were randomly assigned to denosumab (60mg every 6 months) versus placebo. After 36 months, men receiving denosumab significantly increased bone mineral density at all measured sites and decreased risk of vertebral fractures at 36 months following randomization (1.5% versus 3.9%; RR=0.38; 95% CI: 0.19 to 0.78; p=0.006).

Given the uncertainties of management of osteopenia and osteoporosis in prostate cancer patients at risk for bone fractures, referral to physicians who have familiarity with management of osteoporosis should be considered for select patients. These may include endocrinologists, orthopedic surgeons, primary care physicians, or other

specialists who focus on bone heath. Additionally, an uncommon but serious toxicity of bisphosphonates or denosumab is osteonecrosis of the jaw (ONJ). Because men who need dental extractions while on these agents are at higher risk for ONJ, clinicians should consider evaluation by a dentist prior to initiation.

40. Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events. (*Moderate Recommendation; Evidence Level: Grade B*)

Osteoclast-targeted agents were studied in men with mCRPC and bone metastases. In a phase III, double-blind, placebo-controlled trial, Saad et al.[158] randomized patients with mCRPC to receive zoledronic acid at 4mg or placebo every 3 weeks for 15 months; the primary endpoint was the proportion of men experiencing at least 1 SRE. Men receiving zoledronic acid had significantly lower rates of SREs (33% with zoledronic acid versus 44% with placebo; p=0.021) and longer time to first SRE (>410 days with zoledronic acid and 321 days with placebo; p=0.011). The rate of pathologic fractures was also lower compared to placebo (13.1% with zoledronic acid versus 22.1% for placebo). Fizazi et al.[159] performed a non-inferiority trial of 1,904 men with mCRPC with bone metastases randomized to receive denosumab or zoledronic acid with the primary endpoint of outcome of time to SRE. In addition to demonstrating that denosumab was non-inferior to zoledronic acid (20.7 versus 17.1 months; p=0.0002), this trial also showed that denosumab was superior to zoledronic acid in improving time to first SRE in a secondary analysis (p=0.008). Rates of hypocalcemia were higher with denosumab than zolendronic acid; as such, clinicians should monitor calcium levels prior to infusions, and repletion of vitamin D prior to starting these agents, along with SOC calcium and vitamin D maintenance.

In terms of schedule, CALGB 70604[160] was a phase III, open-label trial that randomized 1,822 patients with metastatic breast or prostate cancer (n=686) or multiple myeloma to receive zoledronic acid every 4 weeks or every 12 weeks for 2 years. The trial demonstrated non-inferiority of 12-week dosing intervals for prevention of SREs. No differences were shown for secondary endpoints such as pain scores or performance status or toxicity including ONJ or renal dysfunction.

In the randomized, double-blinded, placebo-controlled phase III CALGB 90202 trial,[161] 645 mHSPC patients were assigned 1:1 to receive either zoledronic acid (4mg intravenously every 4 weeks) or placebo. After progression to CRPC, all patients crossed over to open-label zoledronic acid. Median time to first SRE was 32.5 months in the zoledronic acid group and 29.8 months in the placebo group (HR=0.96; 95% CI: 0.76 to 1.22; p=0.74). OS was similar between groups (HR=0.89; 95% CI: 0.70 to 1.14; p=0.34). The study concluded that early treatment with zoledronic acid in men with HSPC and bone metastases was not associated with lower risk for SREs or death.

FUTURE DIRECTIONS

There are rapid and continued advancements across the spectrum of advanced prostate cancer, and several key areas of future research need emphasis to optimize clinical care and patient-centric outcomes.

Integration of Care

Multidisciplinary care remains a key component of quality care as patients are commonly managed with multimodality approaches involving urologists, medical oncologists, radiation oncologists, radiologists, geneticists, pharmacists, palliative care specialists, and the patient's primary care team. Multidisciplinary clinics and multimodality treatment approaches can optimize treatment selection, maximize results, reduce overtreatment and better manage side-effects.[162] Given the rapidly evolving therapeutic landscape for advanced prostate cancer, these interdisciplinary management discussions will need to include the option to participate in clinical trials locally or through referral to a tertiary center.

Many ongoing clinical trials are evaluating concepts of integrating systemic therapy with radiation and/or surgery assessing the benefit of local therapy in men with metastatic disease or determining the impact of MDT in the oligometastatic setting. The results of these studies are likely to substantially impact the standard approaches to newly diagnosed patients with advanced disease.

Currently, surgical resection of the primary tumor in the setting of metastatic prostate cancer is considered investigational with several retrospective single-arm studies demonstrating safety and feasibility, and many studies from large population-based registries show that

improved survival is associated with local control in metastatic prostate cancer patients.[163-165] However, not all studies have found a survival benefit, and all of these reports should be considered hypothesis-generating as they have unknown biases that make it difficult to apply the data into clinical practice. Several single-arm phase I/II trials and randomized phase II clinical trials have been completed but are yet to be published.[166, 167] The RAMPP trial[168] is a randomized controlled phase II study evaluating the addition of radical prostatectomy to best systemic therapy (BST) in patients with newly diagnosed oligometastatic prostate cancer which demonstrated improved 5 year cancer specific survival in patients randomized to radical prostatectomy plus BST but did not improve clinical progression or OS. Despite its randomized design, the trial was underpowered and prematurely stopped, limiting the strength of its conclusions, but providing hypothesis-generating evidence supporting a potential role for local therapy with surgery in oligometastatic disease.

The phase III RCT SWOG 1802 is evaluating standard systemic therapy with or without local control of the primary in men with hormone-sensitive 'de novo' metastatic prostate cancer. Local control in the SWOG 1802 study may consist of surgery, radiation, or both, based on physician discretion and patient choice. This study aims to address whether local treatment of the primary in the setting of metastatic prostate cancer provides a benefit, with OS as the primary endpoint. In the absence of prospective data demonstrating that surgery leads to an oncologic benefit in men with metastatic prostate cancer, its use should be restricted to clinical trials.

PMSA PET/CT Imaging and Theranostics

PSMA PET imaging can identify sites of prostate cancer with superior specificity and sensitivity compared to conventional imaging and this imaging approach has been widely adopted in the approved indications for newly diagnosed high-risk patients, patients with biochemical failure post local therapy and to establish eligibility for Lutetium-177 PSMA therapy. Ongoing studies seek to provide data to support broader applications including but not limited to treatment response monitoring, guiding MDT in oligometastatic disease and serial imaging to monitor patients with PSA only disease.[169, 170]

These findings are already impacting treatment planning by altering physician decision-making, but they have yet to demonstrate a clear benefit specific to patient outcomes. To date, there is a lack of prospective randomized data evaluating PET as a staging study for untreated prostate cancer, mHSPC or CRPC.[171] What will ultimately determine the role of these PET agents will be trials demonstrating imaging improved patient outcomes as a direct result of earlier intensification of systemic therapies, MDT, and/or prediction of responses to specific therapies.

The role of theranostics in prostate cancer management has evolved rapidly following the approval of Lutetium-177 PSMA based upon the positive results of the VISION and PSMAfore trials in mCRPC.

Research is now turning to its earlier use within the hormone sensitive prostate cancer disease state with the PSMAddition study.

A myriad of novel theranostic agents with a number of different targets are in clinical trials with several actinium-based agents entering into phase III studies. Theranostics is yet another area in which integrated multidisciplinary care will be important and will require the expertise of multiple specialties (e.g., medical oncology, nuclear medicine, radiation oncology).

Metastasis-directed Therapy

Given the ability to identify metastatic sites earlier than was previously possible using newer PET imaging modalities, there has been renewed interest in the concept of MDT with radiation, surgery, or ablative technologies. The majority of data consists of retrospective studies and there are no phase III trials to date.[172] However, in M1 patients with both hormone-sensitive and castration resistant oligometastatic disease several small randomized phase II trials explore the potential benefits of MDT. Utilizing PET choline imaging in 62 patients, the STOMP trial found that median ADT-free survival in mHSPC was 13 months for the surveillance group and 21 months for the MDT group (HR=0.6; 80% CI: 0.40 to 0.90; p=0.11). [173] QOL was comparable at baseline, 3 months, and 1 year of follow-up. In the phase II ORIOLE trial 54 mHPSC patients were randomized to receive stereotactic ablative radiotherapy (SABR) or observation alone using PSMA PET imaging. The primary endpoint was progression after 6 months which was significantly lower with SBRT than with surveillance (19% versus 61%, p=0.005). It was also found that consolidation of all PSMA-positive disease

decreased the risk of new lesions at 6 months (16% versus 63%; p=0.006).[65] In the EXTEND phase II trial, 87 men with oligometastatic hormone sensitive prostate cancer on conventional imaging or F18 PET were randomized to MDT + intermittent hormone therapy or hormone therapy alone and results indicated improved progression free survival in the treatment arm (HR=0.25; 95% CI: 0.12 to 0.55; p<0.001).[174] Two recent phase II trials evaluated outcomes in oligometastatic CRPC, with GROUQ-PCS demonstrating that SBRT + ADT + enzalutamide improved rPFS when compared to ADT + enzalutamide and ARTO showing improved biochemical control and PFS in men treated with SBRT + ADT + abiraterone acetate and prednisone versus ADT + abiraterone acetate and prednisone alone.[40, 128] A recent meta-analysis pooled individual patient data from 7 phase II randomized studies and found improved progression free survival and time to castration resistance.[175] While these results are promising, there remains a lack of data regarding OS as well as selection criteria to identify those patients who will benefit from MDT.

Genomics and Other Systemic Therapies

The steady rate of approval of new agents for use in advanced prostate cancer over the past five years, and the current dearth of comparative studies of these agents heightens the urgency to both identify predictive biomarkers and conduct randomized studies of novel agents with the use of an active control arm (i.e., minimizing the use of the alternative ARPI) to help inform treatment selection.

Currently, the most promising markers are those associated with clinical interventions such as identification of germline or somatic alterations within DDR genes (e.g., BRCA1, BRCA2, and select other DDR mutations) providing evidence for PARP inhibitor use and MSI-H status providing evidence of immune checkpoint inhibitor use.

Multiple trials combining PARP inhibitors plus ARPIs have been published as noted in guideline statements. The optimal use of these therapeutic approaches remains undefined as the vast majority of patients enrolled on these studies had not received prior ARPIs and the toxicity associated with these combinations is not insignificant. Next generation PARP inhibitors such as saruparib, which appears to spare PARP2 and selectively trap PARP1, may provide an improved therapeutic window compared to first generation agents and are being studies in a number of clinical trials.[176]

In addition to novel theranostic agents there are a myriad of classes of agents currently in trial in mCRPC. These include androgen receptor degraders, bispecific T-Cell engagers, CAR-T Cell therapies, epigenetic modulators and pathway inhibitors and antibody-drug conjugates. For the agents undergoing phase III evaluation, there is a trend towards inclusion of active agents (i.e., docetaxel and other approved agents) in the control arms, which hopefully will provide prospective evidence to inform more optimal sequencing of these agents.

Unmet Needs

While the field has witnessed very important progress across the disease spectrum, there remain a myriad of major challenges. Black patients with advanced prostate cancer demonstrate worse outcomes and understanding the societal and biological underpinnings of these disparities remains a critical area for ongoing research.

For patients with metastatic prostate cancer the ultimate unmet need is the inability to cure. While there are several agents approved for use for patients with mCPRC, all have modest impact on OS and compared to the major solid tumors, there is a paucity of comparative data to help clinicians make management decisions based upon prospective evidence. Unlike many other solid tumors advanced prostate cancer is for the most part unresponsive to immune checkpoint inhibition, however a new generation of immune based therapeutics (bispecific antibodies-BiTEs, Chimeric Antigen Receptor- CAR-T cells targeting multiple different prostate targets) are in clinical trials.

Personalized care with predictive markers for treatment selection based on tumor and host biology have not yet been achieved. There has been continued progress toward identification of prognostic markers using molecular markers based on immunohistochemistry and use of genomic signatures, but these have yet to yield predictive results.

While PSMA PET/CT imaging has been broadly adopted, none of our SOC therapeutic interventions for either localized, locally advanced or metastatic disease have been prospectively informed by this imaging modality, although prospective studies across the disease spectrum are ongoing.

Emerging evidence supports the use of SBRT as MDT for oligometastatic prostate cancer although we do not yet have prospective evidence from adequately powered studies that demonstrate improvement in OS.

There are many additional unmet needs. These include studies to inform the potential to de-intensify many of the therapies we use including testosterone suppression, ARPIs and PARP inhibitors in many settings across the disease spectrum. Given the well-known heterogeneity of prostate cancer, the ability to develop individualized approaches to therapeutic management to optimize outcome and minimize toxicity remains one of the highest goals of clinicians who manage this disease.

ABBREVIATIONS

95% CI	95% confidence interval
ADT	Androgen deprivation therapy
AR	Androgen receptor
ARPI	Androgen receptor pathway inhibitor
ART	Androgen receptor-targeted therapy
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AUAER	American Urological Association Education and Research, Inc.
AUROC	Area under the receiver operating characteristic curve
BOD	Board of Directors
BST	Best systemic therapy
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cells
DDR	DNA damage repair
dMMR	Mismatch repair deficient
DXA	Dual x-ray absorptiometry
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
HSPC	Hormone-sensitive prostate cancer
ICECaP	Intermediate clinical endpoints in cancer of the prostate
ISUP	International Society of Urologic Pathologists
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
MDT	Metastasis-directed therapy
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
nmCRPC	Non-metastatic castration-resistant prostate cancer
NNT	Number needed to treat
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-free survival
PET	Positron emission tomography
PGC	Practice Guidelines Committee
PICOTS	Populations, interventions, comparators, outcomes, timing, and settings
PSA	Prostate-specific antigen
PSADT	PSA doubling-time
PSMA	Prostate-specific membrane antigen
QOL	Quality of life
RCT	Randomized controlled trial
rPFS	Radiographic progression-free survival
SOC	Standard of care
SQC	Science & Quality Council
SRE	Skeletal-related event
SUO	Society of Urologic Oncology

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DISCLAIMER

This document was written by the Advanced Prostate Cancer Panel of the American Urological Association Education and Research, Inc., which was created in 2019 and updated in 2023 and 2026. The PGC of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the Panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the evaluation of advanced prostate cancer.

Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ("off label") that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and

use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

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