Approved by the AUA Board of Directors June 2020

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

Note, this document was updated in March 2021 to acknowledge the FDA approval of an additional option for androgen deprivation therapy.

AUA/ASTRO/SUO Guideline

ADVANCED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE
2020

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Purpose

The management of advanced prostate cancer is rapidly evolving. Clinicians are challenged to remain up-to-date and informed with respect to a multitude of treatment options for patients with advanced prostate cancer. 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. 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. 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.

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 other symptom support in advanced prostate cancer patients and encourage engagement with professional or community-based resources, including patient advocacy groups. (Clinical Principle)

Biochemical Recurrence without Metastatic Disease after Exhaustion of Local Treatment Options

Prognosis

4. 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)
5. In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases (e.g., PSADT <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (CT, MRI) and technetium bone scan. (Clinical Principle)
6. Clinicians may utilize novel PET-CT scans (e.g., fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging. (Expert Opinion)

Treatment

7. For patients with a rising PSA after failure of local therapy and no demonstrated metastatic disease by conventional imaging, clinicians should offer observation or clinical trial enrollment. (Clinical Principle)
8. ADT should not be routinely initiated in this population (Expert Opinion). However, if ADT is initiated in the absence of metastatic disease, intermittent ADT may be offered in lieu of continuous ADT. (Conditional Recommendation; Evidence Level: Grade B)

Metastatic Hormone-Sensitive Prostate Cancer

Prognosis

9. Clinicians should assess the extent of metastatic disease (bone, lymph node and visceral metastasis) using conventional imaging in newly diagnosed mHSPC patients. (Clinical Principle)
10. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (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. (Moderate Recommendation: Evidence Level: Grade B)
11. 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)
12. 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 conventional imaging. (Clinical Principle)
13. In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counseling and germline testing. (Expert Opinion)

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)
15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (Strong Recommendation; Evidence Level: Grade A)
16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (Conditional Recommendation; Evidence Level: Grade C)
17. 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)

18. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. (Expert Opinion)

Non-Metastatic Castration-Resistant Prostate Cancer

Prognosis

19. 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)
20. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional imaging at intervals of 6 to 12 months. (Expert Opinion)

Treatment

21. 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)
22. Clinicians may recommend observation with continued ADT to nmCRPC patients, particularly those at lower risk (PSADT >10 months) for developing metastatic disease. (Clinical Principle)
23. 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

24. In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (bone, lymph node, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision making. (Clinical Principle)
25. In mCRPC patients, clinicians should assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy. (Expert Opinion)
26. In patients with mCRPC, clinicians should offer germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status that may inform prognosis and counseling regarding family risk as well as potential targeted therapies. (Expert Opinion)

Treatment

27. In newly diagnosed mCRPC patients, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]/B [docetaxel])
28. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (Conditional Recommendation; Evidence Level: Grade B)
29. 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)
30. In sequencing agents, clinicians should consider prior treatment and consider recommending therapy with an alternative mechanism of action. (Moderate Recommendation; Evidence Level: Grade B)
31. In mCRPC patients who received prior docetaxel chemotherapy with or without prior abiraterone acetate plus prednisone or enzalutamide for the treatment of CRPC, clinicians may offer cabazitaxel. (Conditional Recommendation; Evidence Level: Grade B)
32. In mCRPC patients who received prior docetaxel chemotherapy and abiraterone acetate plus prednisone or

enzalutamide, clinicians should recommend cabazitaxel rather than an alternative androgen pathway directed therapy. (Strong Recommendation; Evidence Level: Grade B)

33. Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (Moderate Recommendation; Evidence Level: Grade C)
34. In patients with mismatch repair deficient or microsatellite instability high mCRPC, clinicians should offer pembrolizumab. (Moderate Recommendation; Evidence Level: Grade C)

Bone Health

35. 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)
36. Clinicians should recommend preventative 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)
37. In advanced prostate cancer patients at high fracture risk due to bone loss, clinicians should recommend preventative treatments with bisphosphonates or denosumab and referral to physicians who have familiarity with the management of osteoporosis when appropriate. (Clinical Principle)
38. 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.

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 hazards ratios 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. After dual review of abstracts and titles, 918 publications were selected for full-text dual review, and 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, hazard ratio (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 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 AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) 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] 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 (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (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.[4]

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

Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• We are 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 Very Low	• Our confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect • We have very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

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		

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.

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.[5] 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.

Background

Epidemiology. Prostate cancer is the most commonly diagnosed solid organ malignancy for men in the U.S. and remains the second leading cause of cancer deaths for this population. Approximately 175,000 new diagnoses of prostate cancer and over 31,000 deaths were estimated in the U.S. in 2019.[6] Importantly, the incidence of metastatic hormone-sensitive prostate cancer (mHSPC) has been increasing in recent years, and recent improvements in survival 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.[7] Furthermore, therapeutic advances in the treatment landscape for mHSPC and mCRPC render treatment decisions and sequencing increasingly complex. It is against this backdrop that the Panel provides evidence-based guidance for treatment of 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

state 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).[8] The patient population covered in this guideline is assumed to have already received local or pelvic therapy, including adjuvant and salvage therapy (i.e., 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 or radiation, the first sign of recurrence is typically a rising PSA in the absence of visible metastases. This is assuming also 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 for optimal treatment approaches is lacking.

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.[9,10] 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 disease 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.[11,12] 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 (PET)-computed tomography (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.[13-15]

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 for men with localized prostate cancer.[16] Additionally, recent press releases state that two of the three approved AR antagonists also improve OS in this population.[17,18] 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.[19,20] Since the approval of docetaxel, multiple

additional agents that show a survival benefit have been FDA-approved on the basis of RCTs.[21-25] 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 ≥2.0 ng/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 (<50 ng/dL). Contemporary lab testing indicates that testosterone levels decline to <20 ng/dL after orchiectomy.[26] Progression may present as either a continuous rise in serum (PSA) levels (values identified at a minimum of 1 week intervals with a minimal value of 2.0ng/mL, 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.[9] **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.[9,27] **High-risk metastatic disease** is defined per the LATITUDE definition for mHSPC 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.[28] **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.[29] **PSA doubling time** (PSADT) is the number of months required for the PSA value to increase two-fold.[30] 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.

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 biochemical recurrence after primary therapy.[31,32] 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,[33,34] 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 owing to the significant differences in sensitivity to detect metastatic disease between conventional and advanced imaging modalities. **Nonetheless, for the purpose of this guideline, the practicing clinician should consider 'metastatic' disease that which is identified on conventional imaging**.

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

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 (<50 ng/dL); progression may present as either a continuous rise in serum PSA levels (values identified 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), 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 ³8, ³3 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

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,[35-38] 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, poly (ADP-ribose) polymerase (PARP) inhibitors[39] and PD-1/PD-L1 inhibitors[40] require the identification of mutations in DNA repair genes and evidence of mismatch repair (MMR) gene defects leading to microsatellite instability, 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. Additionally, the patient's personal goals of care must be carefully considered when making management recommendations. 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) 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 other 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.

Biochemical Recurrence Without Metastatic Disease After Exhaustion of Local Treatment Options

Prognosis

4. **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.[41] 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.[42-45]

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.[46] In addition, time to PSA recurrence and PSA doubling-time 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.[47] 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.

5. **In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases (e.g., PSADT <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (CT, MRI) and technetium bone scan. (Clinical Principle)**

Currently, cross-sectional imaging with CT or MRI along with ^{99m}Tc-methylene diphosphonate bone scintigraphy remain the standard imaging approaches for post-treatment biochemical recurrence, although this is an evolving space. 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).[9,10,28] It should be noted, however, that these modalities infrequently detect metastases in the setting of early PSA recurrence (e.g., PSA <5 ng/mL).[48-50] For example, Kane and colleagues reported that only 14% of patients in a biochemical recurrence cohort had positive CT scans and 9.4% had positive bone scans, with these patients generally having high PSAs and/or rapid PSA kinetics.[48] Only 4.5% of patients with a PSA <10 ng/mL had a positive bone scan. Odewole reported on a cohort of patients

undergoing both CT and ^{18}F-fluciclovine PET for biochemical recurrence, and found that 6 of 29 patients (20.7%) with a PSA ≤5ng/mL had a positive CT finding.[50] In another study, the CT detection rate was 17% for patients with a PSA ≤4 ng/mL.[49]

6. Clinicians may utilize novel PET-CT scans (e.g., fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging. (Expert Opinion)

Novel PET tracers appear to show greater sensitivity than conventional imaging for the detection of prostate cancer recurrence and metastases at low PSA values (<2.0ng/mL). ^{18}F-fluciclovine, the most commonly used radiotracer in the U.S., images amino acid metabolism. The detection of prostate bed recurrences and nodal metastases in patients with biochemically recurrent disease but PSA values still below 1.0 varies between 21 and 72%.[50,51] 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.

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.[52,53] 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.[54] Unlike ^{18}F-fluciclovine, ^{68}Ga-PSMA-11 has not yet received FDA approval in the U.S. Other variants such as ^{18}F-DCFPyl exist and are currently under investigation. Other PET agents such as ^{11}C-choline have FDA approval but suffer from lower sensitivity and specificity for metastatic disease and are no longer in routine use for prostate cancer.[51] 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 novel imaging findings. In addition, oligometastatic disease may be identified, and such patients may be offered management in clinical trials. While such approaches may be intuitively appealing, to date there is only evidence that it may delay initiation of systemic therapy.[55] There is no evidence yet that metastasis directed therapy (MDT) confers a survival benefit.[56]

Treatment

7. For patients with a rising PSA after failure of local therapy and no demonstrated metastatic disease by conventional imaging, clinicians should offer observation or clinical trial enrollment. (Clinical Principle)

While early salvage radiotherapy with or without adjuvant ADT remains the preferred treatment strategy for most men with a biochemical recurrence following prostatectomy, there are currently no systemic treatments with proven efficacy in men without metastatic disease who are not candidates for additional local therapy. The overall course of a rising PSA after failure of local therapy is highly variable, with earlier recurrences indicative of more aggressive disease. In one study of men with biochemical recurrence after salvage radiotherapy, over half of the PSA failures occurred within 18 months of radiation, and these men were at a significantly higher risk of distant metastasis and death compared to men with later PSA recurrences.[57]

Two large observational studies have assessed the question of salvage systemic therapy, and neither found an advantage for earlier treatment in terms of metastasis or survival.[58,59] One study utilized the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database and the other assessed patients cared for in three managed care organizations. In both studies, patients treated with immediate ADT upon biochemical recurrence had a similar mortality risk as those whose ADT was deferred. Notably, a subgroup analysis of men in the managed care study found an apparent survival benefit of early salvage ADT in those with a PSADT of less than nine months. There has been one prospective RCT seeking to compare immediate with delayed ADT (TOAD).[60] While this study did not reach its accrual goals, enrolling 261 of a planned 750 patients, there was a borderline significant improvement in OS with early ADT (HR=0.55; 95%CI 0.30 to 1.00; p=0.050). Given the small sample size and inclusion of some patients who did not receive prior local therapy, these data are insufficient to support a recommendation of early systemic therapy after

biochemical recurrence for most men.

Any potential benefit of early initiation of systemic therapy must also be weighed against the impact of treatment of adverse events and QOL. In the TOAD trial, men in the early ADT arm had higher rates of hormone-treatment-related symptoms and inferior QOL related to sexual activity.[61]

While observation or a clinical trial is preferred, it is recognized that ADT is sometimes given to men with rapid PSA rises in the absence of radiographic metastases in an attempt to delay the appearance of metastases. There is no evidence to determine the best time to start ADT in the absence of radiographic metastases.

8. ADT should not be routinely initiated in this population (Expert Opinion). However, if ADT is initiated in the absence of metastatic disease, intermittent ADT may be offered in lieu of continuous ADT. (Conditional Recommendation; Evidence Level: Grade B)

If men start ADT prior to demonstration of metastatic disease, it is often due to the perception of a higher risk of progression to metastatic prostate cancer based on prognostic criteria such as a higher grade or stage, shorter time to biochemical recurrence, and shorter PSADT.[57,59] Although not recommended, if ADT is initiated in the absence of visible metastases for men who have completed maximal local therapy, intermittent ADT may be offered instead of continuous ADT.

If ADT is initiated, RCTs have 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 >3 ng/mL more than 1 year following primary or salvage radiotherapy for localized prostate cancer.[62] An important limitation of this study to note is the lack of any stratifying criteria or initial risk factors. Intermittent therapy consisted of an 8 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 <4 ng/mL and did not increase more than 1 ng/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.

The open-label EC507 trial (n=109) compared intermittent versus continuous ADT in patients with a PSA increase to ≥1 ng/mL following an initial decrease to <0.5 ng/mL within 3 months of radical prostatectomy.[63] All patients underwent induction with leuprorelin acetate, and patients who achieved a PSA level <0.5 ng/mL during induction were randomized to intermittent versus continuous ADT. In the intermittent therapy arm, ADT was resumed if PSA levels increased to ≥3 ng/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

9. Clinicians should assess the extent of metastatic disease (bone, lymph node and visceral metastasis) using conventional imaging in newly diagnosed mHSPC patients. (Clinical Principle)

The presence and extent of metastatic disease plays 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.[64] As a result, presence of metastatic disease, its burden, and precise locations should be assessed prior to treatment.

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) at the time of diagnosis. As outlined above, 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 31 ng/mL and a range of 0.2 to 798.5 ng/mL.[65] 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.[46] 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 holds great promise. To date, PSMA PET is not routinely available in the U.S.; however, it is of great interest, detects metastatic disease at low PSA values and, therefore, potentially will change 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 1.0 ng/mL were found to have avid lesions in 57% of cases.[66] While this lower level of detection 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.

10. **In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (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. (Moderate Recommendation: Evidence Level: Grade B)**

Irrespective of presentation (i.e., de novo or progression following local curative-intent therapy), patients with metastatic disease should be evaluated with conventional imaging with consideration of chest CT imaging to assess the location and extent of metastatic disease. Although there is no compelling evidence supporting any particular prognostic model for metastatic prostate cancer, there is evidence from prospective randomized trials indicating the utility of defining the extent of disease to help select patients more likely to benefit from the addition of agents such as docetaxel to standard ADT.

In CHAARTED,[67] patients were prospectively defined as having low- or high-volume disease, with high-volume disease defined as 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. The study showed clinical benefit from chemohormonal therapy in prolonging OS, but only in high-volume disease patients (HR= 0.63; 95%CI 0.50 to 0.79; P < .001). No OS benefit observed in patients with low-volume disease (HR= 1.04; 95%CI 0.70 to 1.55; P = .86).

11. **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.[68]

12. **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 conventional 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. For example, 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.[68]

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).[69] Additionally, for studies showing prognostic risk group stratification, PSA or PSA metrics are consistent variables in determination of group assignment.[70-72]

PSA decline after initiation of ADT (nadir) has been shown to be prognostic based on several studies and is useful in patient counselling. 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, ≤4 ng/mL versus >4 ng/mL, risk stratified patients receiving ADT, showing median survivals of 69 months versus 16 months, p<0.0001.[73] 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 three prognostic groups could be identified based on PSA nadir; PSA >4, PSA 0.2-4, and PSA <0.2 with median survivals of 13 months, 44 months, and 75 months, respectively (p<0.001).[74] Obtaining PSA at three to six month intervals allows for determination of the nadir and risk group stratification, and assists in patient counselling 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 ≤0.2 ng/mL versus >4 ng/mL (60.4 months versus 22.2 months, P<.001).[75] 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.[76] 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. At the current time, recommendations are solely for conventional imaging, but as new tracers are introduced they may play a role in disease assessment.

13. In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counseling and germline testing. (Expert Opinion)

There should be consideration of genetic testing for all metastatic hormone-sensitive patients, when possible, regardless of family or personal history of cancer. In a recent study evaluating 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes in a population of men with metastatic prostate cancer and unselected by family history, the prevalence of inherited (germline) DNA repair mutations was 11.8%.[77] Findings of alterations in homologous recombination DNA repair (e.g., BRCA1/2, ATM, Chek2, Rad51D and PALB2) or tumor mutations resulting in microsatellite instability and deficient MMR may have implications in clinical trial eligibility or therapeutics selection (PARP, immunotherapy, or possibly early use of cytotoxic chemotherapy).

Germline testing should include pre-test counselling by someone knowledgeable about the implications of testing. Pre-test counseling needs to 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 counselling with a genetic counselor is necessary for anyone who is found to have one of these mutations.

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 and colleagues in the 1940's.[78] 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.[79] Approval was based on the phase 3 HERO study that showed favorable testosterone suppression and adverse effects of oral relugolix (120 mg/day) compared to leuprolide.[80]

15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (Strong Recommendation; Evidence Level: Grade A)

mHSPC remains an incurable manifestation of the disease. While ADT, with or without nonsteroidal antiandrogens, has been the backbone of mHSPC treatment for many decades, ADT alone is no longer considered sufficient treatment for mHSPC. In just the past five years, multiple studies have shown that additional therapy significantly extends OS and PFS in mHSPC patients.

Docetaxel

Docetaxel is a potent inhibitor of microtubule assembly and disassembly. Since 2015, two clinical trials demonstrated the benefits of adding docetaxel chemotherapy to ADT for mHSPC patients. In the phase III CHAARTED study,[67] 790 patients with mHSPC were equally randomly assigned to receive either ADT in combination with docetaxel (75 mg/m2) for up to 6 cycles or ADT alone. At a median follow-up of 53.7 months, the median OS was 57.6 months for the chemohormonal therapy arm versus 47.2 months for ADT alone (HR=0.72; 95%CI 0.59 to 0.89; P= .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 < .001).

Similarly, in the STAMPEDE trial,[10] 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 (75 mg/m2) 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.

Like many chemotherapy agents, docetaxel has a significant toxicity profile that needs consideration. In the STAMPEDE trial, the most frequently reported adverse events in the SOC plus docetaxel group included febrile neutropenia (15%), general disorder (including lethargy, fever, asthenia—7%), and gastrointestinal disorder (including diarrhea, abdominal pain, constipation, vomiting—8%).[10]

Abiraterone Acetate

Abiraterone acetate is a nonsteroidal irreversible inhibitor of CYP17A1, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA and androstenedione.[81] 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 3 LATITUDE trial,[28] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate (1,000mg daily, given once daily as four 250mg tablets) plus prednisone (5mg daily) or ADT plus placebo. The primary endpoints were OS and radiographic PFS. 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 radiographic PFS 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).

In the STAMPEDE trial,[82] 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1,000mg daily) and prednisolone (5 mg 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[28] 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 a nonsteroidal anti-androgen. 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.[83] In the double-blind, phase 3 TITAN study,[84] 525 patients were assigned to receive apalutamide (240mg daily) with ADT compared to 527 patients receiving placebo plus ADT. Primary endpoints included radiographic PFS and OS. At a median of 22.7 months follow up, the percentage of patients with radiographic PFS 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). Rash of any grade was more common among patients who received apalutamide compared to those who received placebo (27.1% versus 8.5%).

Enzalutamide

Enzalutamide is a novel AR signaling inhibitor. It is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the AR, DNA binding and coactivator recruitment.[85] In the open-label, randomized, phase 3 ENZAMET trial,[86] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide (160mg daily) or a standard nonsteroidal 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 an 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 in this study did not impact on the observed benefit of enzalutamide. This trial did not address the role of early intensification by adding docetaxel to enzalutamide. Several ongoing studies including ARASENS (NCT02799602 docetaxel with/ without darolutamide) will prospectively address this question, until data are available, combination therapy in this setting is not indicated.

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 (160 mg per day) or placebo. All patients also received ADT. The primary endpoint was radiographic PFS. As of October 2018, the risk of radiographic PFS 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<.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.

Both enzalutamide and apalutamide do present a small risk of seizures, so patients with a seizure disorder should instead choose a drug like abiraterone acetate plus prednisone or docetaxel.

Unfortunately, no comparative data on efficacy exist between these four 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. Cost can sometimes be a factor as well when patients

are selecting treatment as some options are costly and not always routinely covered for some patients. Finally, duration of treatment may influence choice. Some patients might prefer a limited 18-week course of docetaxel to daily oral therapy for years. Further, no trials have found a benefit for using both docetaxel and enzalutamide/apalutamide as of yet, though ongoing trials will more directly address this. For now such combinations are not recommended.

In terms of intermittent ADT, SWOG 9346[87] 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 (chemotherapy or androgen receptor-targeted therapy [ART]) added to continuous ADT significantly improves OS, the Panel generally advises against intermittent ADT in otherwise healthy patients with mHSPC.

16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (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, the subgroup analysis for the low-volume group in STAMPEDE Arm H revealed a survival benefit in patients with low-volume metastatic cancer.[64] Given this was a secondary analysis, and that few of the patients had received optimized systemic therapy, the Panel provides a conditional recommendation for ADT plus radiation as an option for patients with minimal metastatic disease willing to undergo the risks associated with local therapy.

The HORRAD trial reported on 432 patients randomized either to ADT alone or ADT with EBRT to the prostate.[88] 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).[64] 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%CI0.52 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= .94).

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 the STAMPEDE trial,[64] no patients had concurrent abiraterone acetate, and only 18% had early docetaxel so no clear recommendation can be made about other drug combinations combined with prostate radiation in the metastatic setting.

17. 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 docetaxel, abiraterone acetate plus prednisone, apalutamide, or enzalutamide **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 (i.e., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[89]

18. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone

acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. (Expert Opinion)

Non-steroidal antiandrogen therapy without ADT in advanced prostate cancer is not recommended. Evidence based on 11 studies encompassing 3,060 patients suggests that use of non-steroidal antiandrogens without ADT compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure, and treatment discontinuation due to adverse events.[90]

Bicalutamide, flutamide and nilutamide are first generation antiandrogens extensively studied in combination with either bilateral orchiectomy or LHRH agonists in mHSPC.[91-95] There is insufficient evidence to support the use of first generation antiandrogens as monotherapy.[91,96-98]

Abiraterone acetate is an inhibitor of CYP17, and apalutamide, darolutamide and enzalutamide are second generation antiandrogens. None of these agents have been studied without ADT for mHSPC, while compelling evidence of survival has been demonstrated with testosterone suppression in combination with either abiraterone acetate plus prednisone, enzalutamide, or apalutamide.[28,82,84,86,99,100] For now, however, these next generation antiandrogens should not be considered without ADT in mHSPC.

Non-Metastatic Castration-Resistant Prostate Cancer

Prognosis

19. 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.[101] 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.[13-15] However, FDA approval of these agents does not specify a doubling time.

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

In addition to monitoring PSA, routine use of conventional imaging should be integrated into monitoring the disease status of men with nmCRPC. The suggested interval of conventional 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.[101] 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.[102] We extrapolate 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

21. 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 2

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 3 SPARTAN trial, Smith et al. randomly assigned 1,207 men in a 2:1 ratio to receive apalutamide (240 mg per day) or placebo.[14] 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 3 study assessing the safety and efficacy of darolutamide in men with nmCRPC.[15] All patients had nmCRPC with a PSADT ≤10 months and PSA ≥2ng/mL (median 9.0 and 9.7 ng/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 placbo 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 3 study evaluating the efficacy and tolerability of enzalutamide in nmCRPC patients.[13] All patients had nmCRPC with a PSADT ≤10 months. The 1,401 patients were randomized (2:1) to enzalutamide 160 mg 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).[103] 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,[104,105] 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 160 mg per day or bicalutamide 50 mg 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 160 mg per day or bicalutamide 50 mg 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 0.34-0.57; p<0.0001).[105]

1The 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).[106] 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.

22. 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.[107] 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.

23. 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

24. In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (bone, lymph node, 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 <20-50ng/dL, higher PSA, and shorter PSADT.[7,36,108-110] There are established imaging findings also known to be associated with increasing risk of mortality. Increasing burden of metastatic disease in the form of the number of metastatic sites is associated with increasing risk of overall mortality.[111] Additionally, there are known relationships between location of metastases and risk of mortality.[112] 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).[113]

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.[36,111,114] Independently, prostate cancer-related pain is known to be strongly associated with the risk of mortality.[37] 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.

25. In mCRPC patients, clinicians should assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy. (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 conventional 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, suggesting that routine imaging can identify a significant portion of patients with radiographic progression who would otherwise not be identified.[102] 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.

26. In patients with mCRPC, clinicians should offer germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status that may inform prognosis and counseling regarding family risk as well as potential targeted therapies. (Expert Opinion)

Germline mutations in genes involved in DNA damage repair (DDR) have been identified in over 11.8% of men with metastatic prostate cancer, with the most commonly identified gene mutations being BRCA2, CHEK2, ATM, and BRCA1.[77] Germline mutations have been found to portend poor prognosis among men with metastatic prostate cancer. Specifically, cancer-specific survival among men found to be harboring a BRCA2 mutation was found to be half of that among men without a defect in DDR (17.4 versus 33.2months, p=0.027).[115] Mutations in tumor suppressor genes have also been found to be associated with adverse outcomes among men with prostate cancer. Specifically, the presence of one or more mutations in tumor suppressor genes was found to be associated with increasing risk of death among men with metastatic disease.

Clinicians should offer germline and somatic testing to inform discussions around prognosis; however, germline testing may also be used to counsel patients regarding their family risk of associated malignancies. 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.

Treatment

27. In newly diagnosed mCRPC patients, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]/B [docetaxel])

Abiraterone acetate plus prednisone, enzalutamide, and docetaxel chemotherapy all have an FDA indication for use in men with mCRPC. For each agent, there is a randomized clinical trial that shows a survival benefit for men with mCRPC.

Abiraterone Acetate

In the placebo-controlled, double-blind, phase 3 COU-AA-302 study, Ryan et al.[116] 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 5 mg twice daily. The primary outcomes of the study were radiographic-PFS and OS. Participants randomized to receive abiraterone acetate plus prednisone had statistically significant improvement in radiographic PFS (HR=0.53 p<0.001), as previously reported during interim analyses.[117] 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).[116] The most common grade 3-4 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 5 mg of prednisone twice daily with either 1,000 mg abiraterone acetate or placebo.[22] 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 3 PREVAIL study, Beer et al. randomized 1,717 chemotherapy-naïve patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily.[118] Co-primary endpoints were radiographic PFS 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 3, double blind AFFIRM study, Scher et al. stratified 1,199 men with CRPC after chemotherapy in a 2:1 ratio to receive enzalutamide (160 mg per day) or placebo.[21] 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, radiographic PFS, and the time to first SRE.

Docetaxel

In the TAX-327 trial, Tannock et al.[19] randomized 1,006 men with mCRPC and good performance status to receive 5mg prednisone twice daily and either docetaxel 75mg/M2 every three weeks, docetaxel 30mg/M2 weekly, or mitoxantrone 12mg/M2 weekly. Patients who received docetaxel plus prednisone every three weeks in TAX-327 had significantly better survival than those receiving mitoxantrone (HR for death: 0.76; p=0.009). Median survival in the docetaxel plus prednisone every three weeks group was 18.9 months compared to 16.5 months in the mitoxantrone group. Analysis at longer follow-up demonstrated the median survival advantage improved slightly to 19.2 months compared to 16.3 months (P=.004).[119] No significant survival differences were noted between the weekly docetaxel plus prednisone group and the mitoxantrone group. In a second study, SWOG 9916 tested docetaxel and estramustine versus mitoxantrone and prednisone for 12 cycles in 674 men with mCRPC.[20] Patients in the docetaxel plus prednisone arm had improvements in median survival (17.5 versus 15.6 months, P=0.02) and time to progression (6.3 versus 3.2 months, p <0.001), and a 20% reduction in risk of death.

The choice of initial treatment in this disease state should be driven by side effect profile and prior treatment. In TAX-327,[19] 26% of patients in the docetaxel plus prednisone every three weeks arm had one or more serious adverse events, and roughly 11% of patients in this group discontinued treatment due to adverse events. In contrast in COU-AA-302,[116] although grade 3-4 mineralocorticoid related adverse events and liver function abnormalities were more common in the abiraterone acetate group, the agent was generally well -tolerated. In PREVAIL, the most common adverse events associated with enzalutamide treatment included fatigue and hypertension.

A second issue is prior treatment. All of the trials above were performed prior to studies demonstrating the efficacy of apalutamide, darolutamide, enzalutamide, abiraterone acetate, and docetaxel in mHSPC and nmCRPC disease states. As such, the choice of subsequent therapy should be influenced by prior therapy, and clinicians should favor treatments that have a different mechanism of action than what was used previously.

28. 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,[23] 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.

29. 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[25] 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 four weeks. Rates of grade 3 or 4 neutropenia and thrombocytopenia were low at 2.2% and 6.3%, respectively.[25]

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 consideration to obtain abdomen/pelvis CT imaging and chest x-ray even in the absence of symptoms prior to cycle 4 (of planned 6 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.[120]

30. In sequencing agents, clinicians should consider prior treatment and consider recommending therapy with an alternative mechanism of action. (Moderate Recommendation; Evidence Level: Grade B)

Optimal sequencing of agents in mCRPC remains an understudied area of research. As most of the agents approved for mCRPC were studied contemporaneously, the control arms typically were inactive agents such as prednisone or mitoxantrone. Furthermore, the only approved agent with a demonstrated survival benefit was docetaxel, so studies of abiraterone acetate and enzalutamide were done in patients either after or before exposure to docetaxel (e.g., COU-AA-301 and COU-AA-302, AFFIRM and PREVAIL, respectively).[21,22,116-118] One conclusion of these trials was that at least the next generation ART therapies abiraterone acetate and enzalutamide clearly have activity both before and after docetaxel chemotherapy.

The largest trial evaluating the sequencing of two ART therapies was performed in Canada and was a randomized phase II trial evaluating the sequence of abiraterone acetate plus prednisone followed by

enzalutamide (group A) versus the opposite sequence (group B).[121] In this trial, 202 patients were randomly assigned to either group A (n=101) or group B (n=101). Time to second PSA progression was longer in group A than in group B (median 19.3 months versus 15.2 months; HR=0.66; 95%CI 0.45 to 0.97; p=0.036). PSA responses to second-line therapy were seen in 36% of patients for enzalutamide and 4% for abiraterone acetate (p<0.0001). This study suggests that abiraterone acetate plus prednisone followed by enzalutamide would be the favored sequence in mCRPC if both agents were used.

AR-V7 has been investigated as a biomarker of possible benefit from sequential ART therapies. In the Prophecy trial,[122] 118 men with mCRPC were enrolled who were starting abiraterone acetate or enzalutamide treatment. AR-V7 detection was independently associated with shorter PFS (HR 1.9 [95% CI, 1.1 to 3.3; P = .032] and 2.4 [95% CI, 1.1 to 5.1; P = .020], respectively) and OS (HR 4.2 [95% CI, 2.1 to 8.5] and 3.5 [95% CI, 1.6 to 8.1], respectively) after adjusting for Circulating Tumor Cells (CTC) number and clinical prognostic factors. Men with AR-V7–positive mCRPC had fewer confirmed PSA responses (0% to 11%) or soft tissue responses (0% to 6%).

31. In mCRPC patients who received prior docetaxel chemotherapy with or without prior abiraterone acetate plus prednisone or enzalutamide for the treatment of CRPC, 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[19] and is generally not recommended for most patients with mCRPC. Docetaxel is an effective option in both mCRPC and mHSPC and should be considered as standard first-line chemotherapy in the setting of mCRPC.[19,20] 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.

Abiraterone acetate and enzalutamide were not available at the time of the TROPIC trial, so it is unknown if this would have influenced the positive outcomes seen in TROPIC. It is also not clear if cabazitaxel given directly after docetaxel would be preferred over using ART therapy next, especially if the patient has never received next generation ART therapies such as abiraterone acetate or enzalutamide.

32. In mCRPC patients who received prior docetaxel chemotherapy and abiraterone acetate plus prednisone or enzalutamide, clinicians should recommend cabazitaxel rather than an alternative androgen pathway directed therapy. (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[123] 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.

33. Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (Moderate Recommendation; Evidence Level: Grade C)

PARP inhibitors leverage defects in DNA repair to provide a survival advantage in men with mCRPC 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.[124] Therefore, inhibition of PARP in these tumors results in cell death.[125]

In the randomized, open-label, phase 3 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 (300 mg twice daily) or the physician's choice of enzalutamide or abiraterone acetate (control).[126] 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 prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A had at least one alteration in BRCA1, BRCA2, or ATM; and cohort B had alterations in any of 12 other prespecified 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 overall survival 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 and a taxane-based chemotherapy. This approval is based on results from the TRITON2 study, which as of the publication of this guideline, are currently only available in abstract form. Other PARP inhibitors (e.g., niraparib, veliparib, talozaparib) are currently under investigation.

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.[127] 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 experiences 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).[127]

34. In patients with mismatch repair deficient or microsatellite instability high 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 microsatellite instability and a hypermutator phenotype that has been associated with chemotherapy resistance but immunotherapy sensitivity.[128]

In a case series of 1,033 patients with advanced prostate cancer 3.1% had a microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR)

prostate cancer, with more than half of those treated with anti PD-1 therapy responding to treatment having a >50% decline in PSA.[129]

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.[130]

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 (i.e., 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.[131,132] 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.

35. 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.[131-133] The Fracture Risk Assessment Tool (https://www.sheffield.ac.uk/FRAX/) is a validated resource to help predict a patient's 10-year probability of hip fracture and the 10-year probability of a major osteoporotic-related fracture (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.[134,135] Several observational studies have assessed changes in bone mineral density.[136-140] 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) 1-year after initiating systemic treatment, and at longer intervals thereafter.

36. Clinicians should recommend preventative 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.[141]

The United States 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.[141] The estimated daily calcium requirement is 1,000 mg to 1,200 mg from food and supplements. The estimated daily vitamin D requirement is 1,000 IU from food, supplements, and sunlight.[141]

37. In advanced prostate cancer patients at high fracture risk due to bone loss, clinicians should recommend preventative 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[142] 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,[143] 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 selected 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.

38. 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.[144] randomized patients with mCRPC to receive zoledronic acid at 4 mg 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.[145] 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[146] 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 osteonecrosis of the jaw or renal dysfunction.

In the randomized, double-blinded, placebo-controlled phase III CALGB 90202 trial,[147] 645 mHSPC patients were assigned 1:1 to receive either zoledronic acid (4mg intravenously every four 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

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with advanced prostate cancer.

Integration of Care

It is now more clear than ever that multimodality approaches and integration of care are critical to improving the care for men with prostate cancer. Multidisciplinary clinics and the resulting multimodality treatment approaches can optimize treatment selection, maximize results and minimize overtreatment and side effects.[148] Many clinical trials are evaluating the concepts of integrating systemic therapy with radiation and/or surgery, such as optimizing treatment of men with locally advanced primary tumors, assessing the benefit of local therapy in men with metastatic disease, or determine the impact of metastasis-directed therapy 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 experimental. There are 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.[149-151] 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 to clinical practice. Several single-arm phase I/II trials and four randomized phase II clinical trials have been completed but are yet to be published.[152,153] While the data mature, there is a Phase III RCT—SWOG 1802—evaluating standard systemic therapy with or without local control of the primary in men with hormone-sensitive 'de novo' metastatic prostate cancer. There are also plans for a surgical treatment arm in the STAMPEDE study (NCT03678025). 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.

Advanced PET Imaging

Advanced PET imaging and theranostics are likely to revolutionize prostate cancer staging and management. Currently ^{11}C-Choline and ^{18}F-fluciclovine are the only FDA-approved PET imaging agents used in the staging of patients with biochemical recurrence or PSA rise after initial therapy, but their role in the management of advanced prostate cancer is not entirely clear. These imaging modalities identify sites of recurrent prostate cancer with superior specificity and sensitivity compared to conventional imaging.[154-156] 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.[157] Use of these imaging agents, along with newer PSMA agents on the horizon, will allow for identification of metastatic sites not otherwise seen with conventional imaging. As a result, it will be important to be cognizant of the stage migration that will occur with advanced PET imaging.

Given the ability to identify metastatic sites earlier than was previously possible, there has been renewed interest in the concept of MDT with radiation, surgery, or ablative technologies. Phase II trials have been designed and executed to determine if there is an impact on the biology of disease. Studies such as the STOMP trial have compared men with newly diagnosed metastatic disease detected on ^{11}C-Choline PET and randomized these men to observation versus MDT. This study was negative for its primary endpoint, but it did demonstrate a prolongation of time to initiation of systemic therapy.[55] Other trials are underway to evaluate this concept and also evaluate its use with concomitant systemic therapy. To date, there is little prospective randomized data evaluating PET as a staging study for untreated prostate cancer, mHSPC or CRPC.[158] While studies are being completed to generate data for FDA registration based on safety and performance, what will ultimately determine the role of these PET agents will be trials demonstrating improved patient outcomes as a direct result of earlier intensification of systemic therapies, MDT, and/or prediction of responses to specific therapies. Until these trials are completed, use of PET imaging beyond identifying visible disease in patients with PSA recurrences is considered experimental.

PSMA-based therapeutics are another potential treatment currently emerging from the ability to target PSMA expressed on the surface of cancer cells. These aim to use the homing ability of PSMA-targeted antibodies or small molecules coupled to radioligands, such as ^{177}Lutetium, to target prostate cancer cells systemically.[159] These are currently under investigation in the advanced, CRPC stages of prostate cancer, but they are likely to move up in clinical trials to mHSPC, biochemical recurrence, and possibly even as neoadjuvant therapy for high-risk localized disease. The

durability of these treatments is being evaluated in multiple prospective clinical studies. This is 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).

Biomarkers and Other Systemic Therapies

Given the dramatic increase in available therapies for advanced prostate cancer over the past 10 years, there is a renewed urgency to identify predictive biomarkers that can guide treatment selection. A number of promising molecular approaches continue to be investigated, but as of yet there is no assay that has been prospectively demonstrated to lead to improved oncologic outcomes.

Currently, the most promising markers are the expression levels of AR-V7 and the identification of germline or somatic alterations in DDR genes such as BRCA1, BRCA2, and ATM. The potential value for assessing these markers stems from the possibility that they can serve as predictive—rather than solely prognostic—biomarkers. That is, there is substantial evidence that these tests might predict differential response to specific systemic therapies, with the implication that pairing these tests with changes in treatment selection could lead to improved long-term outcomes. For AR-V7, the initial seminal study by Antonarakis and colleagues showed that high expression of AR-V7 in CTCs was associated with rapid disease progression in men with mCRPC starting enzalutamide or abiraterone acetate.[160] Other studies have confirmed these findings using different platforms for measuring AR-V7 expression in circulation and also showed that patients with high AR-V7 expression may still respond well to chemotherapy.[161-164] Two CLIA-certified laboratory developed tests are currently commercially available, and the PROPHECY trial prospectively validated these tests in an mCRPC population while also showing that some discrepancies exist in test results between these two assays.[165] Importantly, the vast majority of patients were AR-V7-negative by both assays.

The potential importance of germline and somatic tumor testing, covered in guideline statements 13 and 26, largely surrounds their promise for predicting response to PARP inhibitors such as olaparib, rucaparib, niraparib, veliparib, and talozaparib. Because PARP inhibitors target the DNA replication machinery, tumors with deficiencies in homologous recombination repair (e.g., because of BRCA1, BRCA2 mutations) are uniquely sensitive to PARP inhibition, a phenomenon termed synthetic lethality. In the TOPARP-A trial, heavily-treated mCRPC patients treated with olaparib were much more likely to respond in the setting of a DDR alteration.[39] The response rate was 88% in biomarker positive patients and 6% in biomarker negative patients. From a biomarker standpoint, it is important to note that circulating cell-free DNA may be a future alternative approach for identifying these DDR alterations, and subsequent reversion mutations could be identified after disease progression.[166] In the TOPARP-B study, which assessed 92 patients with DDR aberrations treated with olaparib, 44 patients (48%) demonstrated a confirmed response by imaging, PSA, or CTC criteria.[167] Results of multiple prospective RCTs assessing PARP inhibitors in mCRPC patients with DDR alterations are pending.

In addition to PARP inhibitors, immunotherapies have also emerged as a key therapeutic modality in a large number of solid tumors. Aside from sipuleucil-T, these treatments have generally shown less efficacy in advanced prostate cancer compared to other malignancies, in part related to the relatively low tumor mutational burden of most prostate cancers.[168] However, as described in guideline statement 34, there is likely to be a subset of prostate cancer patients who are uniquely sensitive to immunotherapy— particularly those patients who have tumors that have a high mutational burden (MSI-high).[169] Ongoing trials continue to explore whether immune checkpoint inhibitors, vaccine-based therapies, or oncolytic viruses may have broader utility in men with advanced prostate cancer.

Unmet Needs

While dramatic recent advances have been made, there are many unmet needs in prostate cancer management. Personalized care with predictive markers for treatment selection based on tumor and host biology have not yet been achieved. There has been movement toward identification of prognostic markers and identification of molecular markers based on immunohistochemistry and use of genomic signatures, but these have yet to yield predictive results. A recent example of prognostic ability is the finding that patients with combined defects in tumor suppressor genes (P53, Rb, PTEN) demonstrated improved responses to cabazitaxel plus carboplatin versus cabazitaxel alone in CRPC.[170] Further prospective phase III trials are planned to evaluate the predictive ability of this combined defect for treatment selection. As we move forward as a field, we need to focus on the biologic make-up of tumors and how these can be better leveraged to identify treatment options for patients.

ABBREVIATIONS

95%CI 95% confidence interval
ADT Androgen deprivation therapy
AR Androgen receptor
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
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
SOC Standard of care
SQC Science & Quality Council
SRE Skeletal-related event
SUO Society of Urologic Oncology

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All panel members completed COI disclosures. Those marked with (C) indicate that compensation was received. Disclosures listed include both topic– and non -topic-related relationships. Panel members not listed below have nothing to disclose.

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This document was written by the Advanced Prostate Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2018. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology, oncology, and radiation oncology 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 treatment 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.