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

Note to the Reader:

On July 21, 2014, the FDA issued a recommendation that health care professionals should consider the alcohol content of docetaxel when prescribing or administering the drug to patients.

On July 26, 2013, the FDA issued a safety announcement related to the use of ketoconazole in the form of oral tablets. Side effects can include hepatotoxicity, adrenal insufficiency and dangerous drug interactions.

This document was amended in April 2014 and March 2015 to reflect literature that was released since the original publication of this guideline in May 2013. An additional amendment was conducted in 2018 to reflect new literature released related to the treatment of patients with non-metastatic castration-resistant prostate cancer. This document will continue to be periodically updated to reflect the growing body of literature related to this disease.

CASTRATION-RESISTANT PROSTATE CANCER: AUA GUIDELINE

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Purpose: As a direct result of the significant increase in multiple FDA-approved therapeutic agents for use in patients with metastatic castration-resistant prostate cancer (CRPC), clinicians are challenged with a multitude of treatment options and potential sequencing of these agents that, consequently, make clinical decision-making more complex. To assist in clinical decision-making, six index patients were developed representing the most common clinical scenarios that are encountered in clinical practice. With these patients in mind, guideline statements were developed to provide a rational basis for treatment based on currently available published data.

Methodology: A systematic review and meta-analysis of the published literature was conducted using controlled vocabulary supplemented with keywords relating to the relevant concepts of prostate cancer and castration resistance. The original search strategy was developed and executed by reference librarians and methodologists to create a final evidence report limited to English-language, peer-reviewed literature published between January 1996 and February 2013. This review yielded 303 articles, which were used to inform the statements presented in the guideline as Standards, Recommendations or Options. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions. In April 2014, the CRPC guideline underwent amendment based on an additional literature search, which retrieved additional studies published between February 2013 and February 2014. Thirty-seven studies from this search provided data relevant to the specific treatment modalities for CRPC. In March 2015, the CRPC guideline underwent a second amendment, which incorporated 10 additional studies into the evidence base published through February 2015. A third amendment took place in April 2018 to incorporate additional studies published through April 2018 relevant to non-metastatic CRPC.

Guideline Statements

Index Patient 1

1. Clinicians should offer apalutamide or enzalutamide with continued androgen deprivation to patients with non-metastatic CRPC at high risk for developing metastatic disease. (Standard; Evidence Level Grade A)
2. Clinicians may recommend observation with continued androgen deprivation to patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies. (Recommendation; Evidence Level Grade C)
3. Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (i.e. abiraterone plus prednisone) to select patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies and are unwilling to accept observation. (Option; Evidence Level Grade C)
4. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with non-metastatic CRPC outside the context of a clinical trial. (Recommendation; Evidence Level Grade C)

Index Patient 2

5. Clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and

enzalutamide] /B [docetaxel and sipuleucel-T])

6. Clinicians may offer first- generation anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C)

Index Patient 3

7. Clinicians should offer abiraterone plus prednisone, enzalutamide or docetaxel to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel])
8. Clinicians may offer ketoconazole plus steroid, mitoxantrone or radionuclide therapy to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C [ketoconazole and radionuclide therapy] / B [mitoxantrone])
9. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)
10. Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Index Patient 4

11. Clinicians may offer treatment with abiraterone plus prednisone or enzalutamide to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)
12. Clinicians may offer treatment with ketoconazole plus steroid or radionuclide therapy to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone plus prednisone or enzalutamide. (Option; Evidence Level Grade C)
13. Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to the cancer. (Expert Opinion)
14. Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases. (Expert Opinion)
15. Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Index Patient 5

16. Clinicians should offer treatment with abiraterone plus prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who received prior docetaxel chemotherapy. If the patient received abiraterone plus prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [cabazitaxel])
17. Clinicians may offer ketoconazole plus steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone plus prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)
18. Clinicians may offer retreatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)
19. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

Index Patient 6

20. Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid or radionuclide therapy. (Expert Opinion)

21. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. (Expert Opinion)

Bone Health

22. Clinicians should offer preventative treatment (e.g., supplemental calcium, vitamin D) for fractures and skeletal related events to CRPC patients. (Recommendation; Evidence Level Grade C)
23. Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for mCRPC patients with bony metastases. (Option; Evidence Level Grade C)

Introduction

Incidence and Epidemiology. Prostate cancer is the most commonly diagnosed solid organ malignancy in US men and remains the second leading cause of cancer deaths for this population. Approximately 165,000 new diagnoses of prostate cancer and nearly 30,000 deaths were estimated in the US in 2018.[1] Prostate cancer deaths are typically the result of metastatic castration-resistant prostate cancer (mCRPC), and historically the median survival for men with mCRPC has been less than two years. The recent availability of novel treatments for mCRPC has given a resurgence of hope for these men as studies now demonstrate improved survival with a variety of new agents. However, the unfortunate reality is that mCRPC remains an incurable disease, and it is against this backdrop that we look to the future with cautious optimism and new hope for scientific discovery.

The exact mechanism of transition from castration-sensitive prostate cancer to castration-resistant disease is still not fully understood, but with recent scientific breakthroughs in basic research, there is now a greater understanding. We now know that despite castrate levels of androgens, the androgen receptor (AR) remains active and continues to drive prostate cancer progression.[2,3] This understanding has led to the development of novel agents aimed at further decreasing androgen production or blocking AR function. However, there are also many other biologic pathways that function independent of androgen signaling resulting in CRPC. With a greater understanding of the tumor biology, there is hope for continued development of innovative treatment options that improve survival for men with CRPC.

The treatment of men with CRPC has dramatically changed over the past decade. Prior to 2004, once patients failed primary androgen deprivation, treatments were administered solely for palliation. Landmark articles by Tannock et al.[4] and Petrylak et al.[5] demonstrated that docetaxel improved survival for these patients with mCRPC. Since the approval of docetaxel, six additional agents that show a survival benefit have been FDA-approved on the basis of randomized clinical trials. These have included enzalutamide, abiraterone, and apalutamide, agents designed specifically to affect the androgen axis;[6-8] sipuleucel-T, which stimulates the immune system;[9] cabazitaxel, a chemotherapeutic agent;[10] and radium-223, a radionuclide therapy.[11] These agents have been tested in multiple "disease states" of CRPC to determine if or when patients might benefit from each treatment. Other treatments for men with CRPC have been shown to improve outcomes, but have yet to be approved by the FDA.

Guideline Purpose. As a direct result of the significant increase in multiple FDA-approved therapeutic agents for use in patients with CRPC, clinicians are challenged with a multitude of treatment options and potential sequencing of these agents that, consequently, make clinical decision-making more complex. These Guidelines were developed to provide a rational basis for treatment of patients with CRPC, based on currently available published data. To assist in clinical decision-making, six index patients were developed representing the most common clinical scenarios that are encountered in clinical practice. These index patients were created based on the presence or absence of metastatic disease, the degree of symptoms, the patients' performance status (as defined by the ECOG scale)[i] and the prior treatment with docetaxel-based chemotherapy.

1. Asymptomatic non-metastatic CRPC
2. Asymptomatic or minimally-symptomatic, mCRPC without prior docetaxel chemotherapy
3. Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy
4. Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy
5. Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy
6. Symptomatic, mCRPC with poor performance status and prior docetaxel chemotherapy

Once index patients were developed, the literature was reviewed using the protocol described in the methodology section of this document.

The goal of this Guideline is to provide evidence based recommendations for the treatment of CRPC. Given that this is a rapidly evolving field, this guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. In all cases, the patient's preferences and personal goals should be considered when choosing therapy. Although we are discussing castration-resistant disease, we support the standard of care to maintain castrate testosterone levels even in the face of castration-resistant disease. A flowchart summarizing the guideline statements of this document can be found in Appendix B.

Methodology

Process for Initial Literature Selection. Consistent with the AUA published guideline methodology framework,[12] the process started by conducting a comprehensive systematic review. The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on various therapies for CRPC. The protocol of the systematic review was developed a priori by the methodology team in conjunction with the expert panel. The search strategy was developed and executed by reference librarians and methodologists and spanned across multiple databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials and Scopus. The evidence report was limited to English-language, peer-reviewed literature published between January 1996 and February 2013. Controlled vocabulary supplemented with keywords was used to

[i] Please see Appendix A for the ECOG Performance Status Table

search for the relevant concepts of prostate cancer and castration resistance (biochemical recurrence with a rising PSA and/or progression of disease by radiographic criteria despite a castrate testosterone level). An expert panel manually identified additional references to supplement the electronic search, which were required to meet the same criteria as the previously used studies.

The search strategy focused on commonly used as well as experimental therapies including systemic chemotherapy (estramustine, mitoxantrone, docetaxel, cabazitaxel), immunotherapy (sipuleucel-T) and vaccine therapy, agents targeting the androgen signaling pathway (abiraterone , ketoconazole, corticosteroids, antiandrogens), radiotherapy and radiopharmaceuticals (strontium-89 [Metastron®], samarium- 153 [Quadramet®], radium-223 [Alpharadin®]), antiandrogen withdrawal, bone targeted therapies (zoledronic acid, denosumab), androgen receptor inhibitor (enzalutamide), palliative care and experimental therapy, (CYP-17 inhibitor [TAK700], cMET/VEGFR inhibitor [cabozantanib]).

The outcomes of interest were a priori determined by the panel based on their respective importance to patients, recognizing that some of these endpoints are surrogates for the patients and included overall survival (OS), progression-free survival (PFS), metastasis-free survival, PSA PFS, PSA decline, measurable disease response, adverse events/side-effects of treatment, quality of life (QOL), skeletal-related events (SREs), pain-free survival, and pain response.

The methodology team independently rated the methodological quality of the studies and provided an overall judgment of the whole body of evidence based on confidence in the available estimates of effect.

The methodology team summarized the data with explicit description of study characteristics, methodological quality, main findings and the quality of the evidence (confidence in the estimates). The methodology team attended panel meetings and facilitated incorporation of the evidence into the guideline.

Quality of Individual Studies and Determination of Evidence Strength. The systematic review included 303 eligible studies that addressed the pre-identified questions of interest. A large body of evidence evaluated established chemotherapy agents such as docetaxel [19 Randomized controlled trials (RCTs)], estramustine (5 RCTs) and mitoxantrone (5 RCTs). Randomized evidence was also available for various immunotherapies (8 RCTs), therapies targeting the androgen signaling pathway (12 RCTs), radiotherapy and radiopharmaceuticals (4 RCTs) and bone-targeting therapies (6 RCTs). The quality of these trials was acceptable overall and ranged from moderate to low risk of bias. All the remaining studies were otherwise non-randomized (observational) and considered to be at high risk of bias.

The quality of the evidence (confidence in the estimates) was limited in many studies by indirectness. Indirectness occurs when studies use surrogate endpoints that depend on laboratory or radiographic measurements (PSA free survival, PSA decline or PFS based on imaging).[13] These outcomes usually are surrogates for other important patient outcomes more essential for decision making, such as mortality, pain and QOL. Imprecision (wide confidence intervals due to small number of events) was also common in most CRPC trials and can lower the confidence in the provided estimates.

Limitations of the Literature. The systematic review and guideline process identified clear gaps in the available evidence base. None of the therapies identified in this review were curative or resulted in long term remission. Therefore, primary research on new agents is clearly needed for this important and common condition. Future trials should also use and incorporate patient reported outcomes, such as QOL and pain control. The current evidence base suffers from imprecision that can be overcome by multi-site RCT collaboration or prospective (pre-planned) meta-analyses.

Guideline Amendments. In April 2014 and March 2015, the CRPC guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines in an effort to maintain currency. An additional amendment took place in April 2018 related specifically to patients with non-metastatic CRPC (Index Patient 1). The amendments allowed for the incorporation of additional literature released since the initial publication of this guideline in 2013. Comprehensive searches of several databases from February 2013 to February 2014 (2014 amendment), February 2014 to February 2015 (2015 amendment), and February 2015 to April 2018 (2018 amendment, specific to non-metastatic CRPC patients), English language, were conducted. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies on therapy for CRPC.

The 2014 search yielded 998 references, of which 662 were excluded after duplicate abstract and title review. Full text was retrieved for the 336 included studies. Eventually, 37 studies provided relevant data on the specific treatment modalities for CRPC. The resulting amendment focused on the incorporation of literature relevant to the use of radium-223 in the treatment of men with mCRPC.

The 2015 search yielded 1,150 references, of which 1,090 were excluded after duplicate abstract and title review. Full texts were retrieved for 60 included studies. Eventually, 10 studies (published in 14 manuscripts) provided relevant data on the specific treatment modalities for CRPC. The resulting amendment focused on the incorporation of additional information on the use of enzalutamide in chemo-naïve patients as well as the use of abiraterone plus prednisone.

The 2018 search yielded 770 references, of which 700

were excluded after abstract and title screening. Full texts were retrieved for 70 studies. Eventually, 47 studies that provided relevant data were included for data abstraction. Of those, five contained data specific to non-metastatic CRPC and were included in the final update report. The resulting amendment focused on the incorporation of additional information on the treatment of non-metastatic CRPC patients.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1).[12] The framework of rating the quality of evidence is an adaptation and modification[12] of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation).[13,14] In this adaptation, the AUA rates the quality of evidence as high, moderate or low (A, B or C). Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/ burdens appears relatively equal or appears unclear; Options may be supported by Grade A, B or C evidence. It is important to note that grading (A, B or C) does not reflect the magnitude of a potential benefit or harm, but is instead related to the methodological review of the study. For some clinical issues, there was little or no evidence from which to construct evidence-based statements. 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 existed among Panel members.[15] 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 and for which there is no evidence. The completed evidence report may be requested through AUA.

Panel Selection and Peer Review Process. The Panel was created by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members, all of whom have specific expertise with regard to the guideline subject to include both urologists and medical oncologists.

Once nominated, panel members are asked to record their conflict of interest (COI) statements, providing specific details on the AUA interactive web site. These details are first reviewed by the Guidelines Oversight Committee (GOC), a member sub-committee from the PGC consisting of the Vice Chair of the PGC and two other members. The GOC determines whether the individual has potential conflicts related to the guideline. If there are no conflicts, then the nominee's COI is reviewed and approved by the AUA Judicial and Ethics (J&E) committee. A majority of panel members may not have relationships relevant to the guideline topic.

Table 1: AUA Nomenclature Linking Statement Type to Evidence Strength

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/ burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence
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 is no evidence

The AUA conducted an extensive peer review process. The initial draft of this Guideline was distributed to 56 peer reviewers of varying backgrounds; 30 responded with comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the PGC. It was then submitted to the AUA Board of Directors for final approval. All subsequent amendments also underwent approval by the PGC, Science and Quality Council, and Board of Directors. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work.

Index Patient 1

Asymptomatic non-metastatic CRPC

One of the first clinical presentations of CRPC occurs in a patient with a rising PSA despite medical or surgical castration. This is typically defined as a patient with a rising PSA and no radiologic evidence of metastatic prostate cancer. The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) defines PSA only failure as a rising PSA that is greater than 2ng/mL higher than the

nadir; the rise has to be at least 25% over nadir, and the rise has to be confirmed by a second PSA at least three weeks later. In addition, the patient is required to have castrate levels of testosterone (less than 50 ng/dL) and no radiographic evidence of metastatic disease.[16] These patients represent a relatively common clinical presentation and the earliest clinical manifestation of castration resistance.

Guideline Statement 1.

Clinicians should offer apalutamide or enzalutamide with continued androgen deprivation to patients with non-metastatic CRPC at high risk for developing metastatic disease. (Standard; Evidence Level Grade A)

Until recently, no agent had demonstrated significant benefits in large Phase 3 trials in the non-metastatic CRPC patient population. In February 2018, apalutamide became the first FDA-approved treatment for patients with non-metastatic disease. In addition, enzalutamide has also been shown to offer benefits in this patient population with FDA approval granted in July 2018.

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. It has a 7- to 10- fold greater affinity for the AR compared to bicalutamide, a first-generation anti-androgen.[17]

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.[8] All patients had a diagnosis of non-metastatic CRPC with a PSA doubling time ≤10 months and continued on androgen deprivation therapy (ADT). At the time of planned primary analysis, median metastasis-free survival (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). Note, given the time required for maturation of OS data in such trials, MFS is now a commonly used surrogate endpoint defined as time from randomization to date of first evidence of recorded distant metastases or death, whichever occurred first. Additionally, 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 progression-free survival 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 (30.4 versus 21.1%), hypertension (24.8% versus 19.8%), rash (23.8% versus 5.5%), diarrhea (20.3% versus 15.1%), nausea (18.1% versus 15.8%), weight loss (16.1% versus 6.3%), arthralgia (15.9% versus 7.5%), and falls (15.6% versus 9.0%). Other adverse events of interest included fracture (11.7% versus 6.5%), dizziness (9.3% versus 6.3%), hypothyroidism (8.1% versus 2.0%), mental-impairment disorder (5.1% versus 3.0%), and seizure (0.2% versus 0%). Of note, events related to hypothyroidism were all grade 1 or 2, were generally identified early following initiation of apalutamide treatment, and were managed with medical therapy. Particular attention should be paid to monitoring thyroid stimulating hormone (TSH) in individuals with known hypothyroidism given observed changes in thyroid function with apalutamide treatment.

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.[18] This drug binds AR with a five- to eight-fold higher affinity than bicalutamide.[18]

PROSPER is a randomized, double-blind, placebo-controlled, Phase 3 study (currently only available in abstract form) evaluating the efficacy and safety of enzalutamide in non-metastatic CRPC patients.[19] All patients had M0 CRPC with a PSA doubling time ≤10 months (median PSA doubling time, 3.7 months) and PSA ≥2ng/mL. 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; however, there was a 20% reduction in the relative risk of death with enzalutamide compared to placebo. 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 with a 93% reduction in the relative risk of PSA progression (37.2 months in the enzalutamide group compared to 3.9 months in the placebo group; HR= 0.07; P<0.001). 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.

In the STRIVE trial, 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.[20] Both arms remained on ADT. While the treatment effect of enzalutamide on PFS was consistently favorable across all patient populations, 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). OS was not reported. Common adverse events reported more frequently in the enzalutamide group included fatigue, back pain, hot flashes, falls, hypertension, dizziness, and decreased appetite.

Guideline Statement 2.

Clinicians may recommend observation with continued androgen deprivation to patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies. (Recommendation; Evidence Level Grade C)

Since all agents have potential side effects and only the standard therapies have demonstrated evidence of benefit, it is the panel judgment that no treatment (i.e. observation) other than continued ADT be recommended for patients who do not want or cannot have a standard therapy. Given the lack of data showing that any treatment other than the standard therapies in this disease setting meaningfully impacts clinical outcome, it is the panel opinion that such patients should be encouraged to enter clinical trials, when available.

Guideline Statement 3.

Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (i.e. abiraterone plus prednisone) to select patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies and are unwilling to accept observation. (Option; Evidence Level Grade C)

There may exist a subset of patients who do not want or cannot have a standard therapy and are uncomfortable with treatment with systematic ADT alone. Such patients may wish to initiate additional treatment despite the lack of good evidence with regards to benefits and harms in this setting. For such patients, clinicians may offer abiraterone plus prednisone as an option that has shown superior survival benefits in metastatic CRPC and metastatic high-risk castration-sensitive prostate cancer.

Abiraterone: Abiraterone is an irreversible inhibitor of the hydroxylase and lyase activities of CYP17A, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA and androstenedione.[21] While abiraterone is considered a standard therapy in other patient populations, it is not FDA-approved for non-metastatic patients. This agent was recently FDA-approved in combination with prednisone for the treatment of men with metastatic high-risk castration-sensitive prostate cancer. Prior to this, it was initially FDA-approved for patients with metastatic CRPC who had received prior chemotherapy; the indication was then expanded for patients with mCRPC prior to chemotherapy. Though it is generally well tolerated and is associated with fewer serious adverse events compared to other available therapies, such as ketoconazole or first-generation anti-androgens, abiraterone is associated with expected increases in mineralocorticoids upstream of CYP17A, accounting for the treatment-related side effects, such as hypertension, hypokalemia, edema and fatigue that respond to low dose glucocorticoids. Use of abiraterone in combination with low-dose prednisone is required to manage these treatment-related increases in ACTH and attendant side effects.

Prior to potential initiation of abiraterone therapy in this patient population, clinicians should consider a careful discussion of risks/benefits with patients, particularly those with significant baseline comorbidities. The evidence for this index patient is rated Grade C due to a lack of significant long-term data in this specific population showing survival benefits.

Guideline statement 4.

Clinicians should not offer systemic chemotherapy or immunotherapy to patients with non-metastatic CRPC outside the context of a clinical trial. (Recommendation; Evidence Level Grade C)

The past few years have seen a plethora of new treatments for men with mCRPC. Indeed, multiple agents (e.g., docetaxel, various checkpoint inhibitors) have been shown to prolong survival for men with mCRPC. Only some agents have been studied in this patient population and shown clinical benefit. Thus, the panel strongly recommends against this practice due to a lack of outcome data in the non-metastatic disease setting.

Of the classes of agents recommended against, only denosumab has been systematically studied in this non-metastatic state. Denosumab 120 mg subcutaneously monthly, which in a placebo-controlled randomized trial,[22] was shown to modestly delay the development of radiographically detected bone metastases, but it did not impact QOL or OS. This agent showed only a modest delay in bone metastases of three months and was specifically denied approval by the FDA for this indication. It was associated with significant side-effects, including osteonecrosis of the jaw. Thus, monthly denosumab is not indicated for non-metastatic CRPC.

Thus, the primary reason the panel recommends against the routine use of these agents in this patient population is concerns about toxicity. All of the agents not recommended have the potential for significant

toxicity. While this toxicity may be greater for some classes (i.e. chemotherapy) than others, all of these agents have the potential to harm patients. Thus, the combination of no known benefit with known and potentially serious harms results in a recommendation not to use these agents.

Index Patient 2

Asymptomatic or minimally symptomatic, mCRPC without prior docetaxel chemotherapy

This patient represents a common clinical presentation seen in the CRPC setting today. These patients are characterized as having a rising PSA in the setting of castrate levels of testosterone, documented metastatic disease on radiographic imaging and no prior treatment with docetaxel chemotherapy for CRPC. The key distinction between this patient and Index Patients 3 and 4 is symptom status. Specifically, this patient is defined as having no symptoms or mild symptoms attributable to his prostate cancer. However, one must then consider whether the patient requires regular opioid pain medications for symptoms thought to be attributable to documented metastases to achieve this level of pain control. In general, if patients require regular narcotic medications for pain relief, they are not included in this category. Acknowledging these important definitions, the panel makes the following guidelines statements:

Guideline statement 5.

Clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel and sipuleucel-T])

Abiraterone plus prednisone, enzalutamide, docetaxel chemotherapy and sipuleucel-T immunotherapy are currently the only agents that have an FDA indication for use in men with mCRPC who have not yet received docetaxel chemotherapy. For each agent, there is a randomized clinical trial that shows a survival benefit for the drug.

Abiraterone: Prior to docetaxel chemotherapy, abiraterone plus prednisone has demonstrated an improvement in radiographic PFS and OS. In the COU-AA-302 study, Ryan et al.[23,24] randomized 1,088 men with mCRPC who had not received prior chemotherapy to receive either abiraterone 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-progression free and OS. Participants randomized to receive abiraterone plus prednisone had statistically significant improvement in radiographic progression-free survival (HR=0.53 p<0.001), as previously reported during interim analyses.[23] The final analysis of OS showed a statistically significant increase in patients treated with abiraterone plus prednisone (HR=0.81; 95% CI, 0.70 to 0.93; P=0.0033).[24] Although grade 3-4 mineralocorticoid related adverse events and liver function abnormalities were more common in the abiraterone group, the agent was generally well-tolerated.

Enzalutamide: In the double-blind, phase 3 PREVAIL study, Beer et al. randomized 1,717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily.[25] Eligible patients were asymptomatic or mildly symptomatic and had not received cytotoxic chemotherapy, ketoconazole, or abiraterone. 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) and delayed 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. Overall, the most common adverse events associated with enzalutamide treatment included fatigue and hypertension.

Docetaxel: Docetaxel is a potent inhibitor of microtubule assembly and disassembly. In the TAX-327 trial, Tannock et al.[4] randomized 1,006 men with mCRPC and good performance status to receive 5mg prednisone twice daily and either docetaxel 75mg/M^2 every three weeks; docetaxel 30mg/M^2 weekly or; mitoxantrone 12mg/M^2 weekly. As the primary outcome of this trial was survival, mitoxantrone effectively served as a "placebo" arm, as a prior RCT showed symptom improvement but failed to show a survival advantage associated with mitoxantrone when compared to placebo.[26] Patients who received docetaxel plus prednisone every three weeks in TAX-327 had significantly better survival than those receiving mitoxantrone (HR for death: 0.75; 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. No significant survival differences were noted between the weekly docetaxel plus prednisone group and the mitoxantrone group. While this study provides strong evidence to support the use of docetaxel plus prednisone in men with mCRPC, there are two important caveats to bear in mind, particularly when comparing it to later studies on newer agents. First, this study did include many patients with symptomatic mCRPC (Index Patient 3). Second, 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 a second study, SWOG 9916 tested docetaxel and estramustine v. mitoxantrone and prednisone for 12 cycles in 674 men with mCRPC.[5] Patients in the docetaxel plus prednisone arm had improvements in median survival (17.5 v. 15.6 months, p=0.02) and time to progression (TTP) (6.3 v. 3.2 months, p <0.001) and a 20% reduction in risk of death. The side effect profile associated with docetaxel may lead patients to delay docetaxel treatment until symptomatic or to elect not to receive this treatment at all. A thorough discussion of the risks and benefits of this treatment is warranted with all patients who are considering this therapy.

Sipuleucel-T: Sipuleucel-T is an approved 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, published in 2010.[9] 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; 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.

In summary, abiraterone plus prednisone, enzalutamide, docetaxel and sipuleucel-T are considered standard therapies in this index patient. Unfortunately, there are no direct studies comparing the agents that can be used to inform optimal sequencing. As a general principle, it is preferable to give the least toxic agent first, particularly given the lack of head-to-head data, but this must be deliberated in light of other considerations, including convenience of administration. As such, patients should be informed of all options and be allowed to make an informed decision based upon their own preferences and goals related to therapy.

Guideline Statement 6.

Clinicians may offer first- generation anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C)

Manipulation with existing anti-androgen agents, such as bicalutamide, nilutamide or flutamide, or ketoconazole plus steroid can only be considered an option in this setting, if only because they offer patients who do not want or cannot have one of the standard therapies a relatively less toxic therapeutic option.

In patients who elect not to receive the standard therapies, there are a number of other options available. Data to support the use of these options in the setting of asymptomatic or minimally-symptomatic prostate cancer is limited and generally of lesser strength than the standard treatments. Some have suggested that the removal of anti-androgen therapy may have a beneficial effect on mCRPC. The majority of these studies supporting this approach are observational.[27-29] The single RCT addressing this issue failed to show any survival benefit associated with anti-androgen withdrawal.[30]

Anti-androgens: Though anti-androgens (flutamide, bicalutamide and nilutamide) are commonly used, these agents can be associated with side effects including gastrointestinal upset and liver toxicity.

Ketoconazole: The oral androgen synthesis inhibitor ketoconazole is a weak inhibitor of CYP11A and CYP17A and suppresses the synthesis of adrenal and tumor tissue androgens. Ketoconazole can be associated with nausea and hepatotoxicity and must be given with replacement steroids.

Finally, some patients may not wish to pursue any therapy, waiting for the onset of symptoms to pursue treatment (if they were to ever elect treatment at all). Given current data in this patient population, this approach is a reasonable option. In all cases, the patient's preferences and personal goals should be considered when choosing therapy for asymptomatic or minimally symptomatic CRPC.

Index Patient 3

Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy

These patients have a rising PSA in the setting of castrate levels of testosterone, documented symptomatic metastatic disease on radiographic imaging and no prior history of docetaxel chemotherapy for prostate cancer. The definition of symptomatic disease warrants additional explanation to contrast with Index Patient 2. First, the patient must have symptoms that are clearly attributable to the metastatic disease burden, not any other medical condition. Second, if having pain, the patient should require regular opiate pain medications for symptoms attributable to documented metastases in order to achieve an acceptable level of pain control. If patients require regular narcotic medications for pain relief, then they are symptomatic from their prostate cancer and should be included in this category.

Guideline Statement 7.

Clinicians should offer abiraterone plus prednisone, enzalutamide or docetaxel to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel])

Abiraterone: In the previously discussed COU-AA-302 study, treatment with abiraterone prolonged OS compared to prednisone alone in both a clinically and statistically significant manner after a median follow-up of over four years. The results support the favorable safety profile of abiraterone in chemotherapy-naïve mCRPC patients.[24] While the randomized phase-III trial was only conducted in asymptomatic and minimally symptomatic men, the mechanism of action of abiraterone is similar to that of ketoconazole and has shown marked palliative and skeletal related benefits. Abiraterone is FDA approved for treatment of a symptomatic patient population, and the label specifies only that it is for the treatment of mCRPC; therefore, it

is appropriate for Index Patient 3.

Enzalutamide: As previously noted, the PREVAIL study showed that enzalutamide significantly decreased the risk of both radiographic progression and death in chemotherapy-naïve men in whom the disease progressed despite androgen deprivation therapy. The study was stopped after a planned interim analysis that showed the benefit of the drug with respect to all secondary endpoints, including time until the initiation of chemotherapy, the time until the first skeletal-related event, a complete or partial soft-tissue response, the time until PSA progression and a rate of decline of at least 50% in PSA.[25]

Docetaxel: As previously noted, the TAX-327 and SWOG-9916 studies support the use of first-line docetaxel every three weeks with daily prednisone in symptomatic mCRPC.[4,5] Bone pain responses were more significant in docetaxel patients (35% v. 22%; p=0.08), as were improvements in QOL compared to the mitoxantrone group. Updated results showed a similar median survival benefit for docetaxel every three weeks v. mitoxantrone, with three-year survival rates of 18.6% and 13.5%, respectively (p=0.005).[31] The magnitude of benefit associated with docetaxel plus prednisone treatment for CRPC was independent of age, performance status or baseline PSA.

Guideline Statement 8.

Clinicians may offer ketoconazole plus steroid, mitoxantrone or radionuclide therapy to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C [ketoconazole] / B [mitoxantrone] / C [radionuclide therapy])

Ketoconazole: Ketoconazole has not shown significant OS improvements in patients with symptomatic, chemotherapy-naive mCPRC. Ketoconazole has substantial treatment-related side effects that have prompted the development of more potent CYP17A inhibitors, such as abiraterone.

Mitoxantrone: Mitoxantrone, a topoisomerase inhibitor, has not shown a survival benefit compared to docetaxel -based chemotherapy regimens in mCRPC, as previously discussed.[4] Mitoxantrone is primarily utilized in symptomatic mCRPC patients with poor performance status (i.e. not candidates for docetaxel-based chemotherapy). In support of its use, mitoxantrone has been shown to provide a palliative response in symptomatic patients. In one study by Tannock et al. mitoxantrone was observed to provide significant palliative care in 29% of patients who received mitoxantrone plus prednisone, as compared to 12% who received prednisone alone (P = 0.01).[26]

Radionuclide Therapy: The use of systemic radiotherapy with samarium-153 or strontium-89 occasionally benefits patients with widely metastatic, symptomatic bone involvement; however, this therapy is usually reserved for candidates who are not responding to palliative chemotherapy and who are not candidates for localized external beam radiotherapy (EBRT).[32,33] The risk of bone marrow suppression, which might influence the ability to administer systemic chemotherapy agents, should be considered before initiation of radionuclide therapy. The use of samarium-153 is further discussed for use in Index Patient 6.

Guideline Statement 9.

Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

Radium-223: 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 on 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 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 v. 11.3 months (HR=0.695, 95% CI 0.581 to 0.832; P=0.00007) in favor of radium-223 over placebo. Time to first SRE improved from 9.8 month with placebo to 15.6 months with radium-223 (HR=0.658, 95% CI 0.522 to 0.830; P=0.00037). 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 six intravenous injections with a dose of 50 kBq per kilogram of body weight every four weeks.[11] Rates of grade 3 or 4 neutropenia and thrombocytopenia were low at 2.2% and 6.3%, respectively.[34]

Guideline Statement 10.

Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Estramustine: Estramustine has both cytotoxic and hormonal effects, although the major mechanism of action is as an alkylating agent, which has not shown significant OS advantages. Petrylak et al. showed an OS of 17.5 months for docetaxel plus estramustine compared to 15.6 months for mitoxantrone plus prednisone (P=0.02).[5] However, the survival advantage was similar to Tannock et al for docetaxel without estramustine. Therefore the advantage has been attributed to docetaxel. Given the significant toxicity

with estramustine, its use cannot be encouraged.[4] A variety of secondary hormonal deprivation strategies have been studied after failure of initial ADT in mCRPC, such as anti-androgen withdrawal, administration of alternative anti-androgens and use of estrogen derivatives, such as diethylstilbesterol (DES) and estramustine; however, none of these strategies have demonstrated significantly improved OS in the symptomatic, pre-chemotherapy mCRPC setting.

Sipuleucel-T: The use of sipuleucel-T immunotherapy is not recommended in symptomatic disease that necessitates narcotic use, consistent with the FDA indication for this compound. Thus, sipuleucel-T currently may be considered only for patients with asymptomatic or minimally symptomatic mCRPC and is most appropriate for Index Patient 2, as previously discussed.[9] Patients with large tumor burdens, those with visceral disease and those with more aggressive disease (predicted survival < 12 months) are less likely to respond to immunotherapy.

Index Patient 4

Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy

Clinical trials have generally excluded patients with a poor performance status (ECOG 3-4) from participation. Thus, most data regarding management of such patients is extrapolated from randomized trials of eligible patients who had a better performance status, as well as from some smaller trials and registries. Even a Phase 3 clinical trial that was presumptively designed for a population considered "unfit" for docetaxel (ALSYMPCA to evaluate radium-223) still only allowed a performance status of ECOG 0-1. However, treatments with acceptable safety profiles do exist and should be considered, even in poor performance status patients. This is especially true in those patients in whom the poor performance status may be considered to be directly related to the cancer itself and thus whose status might improve with effective treatment. Treatments must be individually tailored in these patients after a careful discussion of risks and benefits with particular attention to patient QOL.

Guideline Statement 11.

Clinicians may offer treatment with abiraterone plus prednisone or enzalutamide to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)

The FDA approved the label for use of abiraterone plus prednisone in mCRPC independent of docetaxel treatment following interim analysis of data from the previously discussed COU-AA-302 study.[23] Follow up analysis did show significant improvements in OS.[24] Notably, COU-AA-302 was administered only in good performance status patients, but it is the panel's opinion that abiraterone plus prednisone would be a reasonable alternative to chemotherapy for patients even with a poor performance status.

Please refer to Index Patients 1, 2, and 3 for further discussion of enzalutamide.

Guideline Statement 12.

Clinicians may offer treatment with ketoconazole plus steroid or radionuclide therapy to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone plus prednisone or enzalutamide. (Option; Evidence Level Grade C)

Ketoconazole: Ketoconazole has been demonstrated to have anti-cancer effects[30] in the setting of mCRPC and could be a viable alternative, in particular if abiraterone plus prednisone is unavailable. It is important to recognize that ketoconazole has a worse side effect profile, as previously stated in the discussion of Index Patient 1.

Radionuclide Therapy: Samarium-153 and strontium-89 have not shown a survival benefit but may offer palliative benefit in patients symptomatic with bone pain. These are further discussed under Index Patient 6. The use of radium-223 in this Index Patient is addressed below.

Guideline Statement 13.

Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to the cancer. (Expert Opinion)

Patients with mCRPC may have a poor performance status for multiple reasons, but the two major possibilities are related to the cancer itself or because of non-prostate cancer related causes. For instance, a patient who was previously active and healthy whose cancer progresses rapidly in bone and liver may develop severe pain, weakness, weight loss and other symptoms thought to be directly related to the progression of cancer. This patient may benefit from treatment. An alternative patient may be one in whom a long history of chronic disorders, such as diabetes, heart disease, arthritis, cirrhosis and other conditions may be underlying the new diagnosis of prostate cancer. In this case, effective treatment of his cancer would not improve any of his underlying conditions.

Docetaxel: Docetaxel is considered the standard first-line therapy in mCRPC and has demonstrated both a survival benefit as well as a palliative benefit in symptomatic disease. Most patients with a poor performance status are not considered qualified candidates for chemotherapy, but it is possible that some patients whose cancers are mostly contributing to their disability may benefit from anti-cancer treatment. Such an approach must be undertaken cautiously by a qualified physician experienced in the administration of chemotherapy. Dosage and schedule modifications might be considered for individual patients to make this more tolerable.

Mitoxantrone: Mitoxantrone was approved in 1996 based on two randomized trials that demonstrated a palliative benefit in symptomatic mCRPC.[26,35] No survival benefit has been seen with mitoxantrone. However, it could be considered as an alternative option to docetaxel or potentially as a second-line therapy in men with symptomatic disease and a poor performance status. Like all of the trials mentioned, no clinical trials allowed patients with poor performance status, so caution must be taken. If the poor performance status is not related to cancer progression, then systemic chemotherapy of any kind is not recommended.

Guideline Statement 14.

Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases. (Expert Opinion)

Radium-223 may be offered for patients with symptomatic bone pain and non-visceral metastases. Radium-223 has showed survival benefit in patients with good performance status. If it is believed that the poor performance status of Index Patient 4 is due to symptomatic bone pain, radium-223 may also be beneficial to these patients.

Guideline Statement 15.

Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

In subsequent analyses of the IMPACT trial, it appears that the survival benefit associated with its use does not appear until six months after therapy.[9] Sipuleucel-T appears to benefit patients with a lower disease burden and better performance status. Most patients in IMPACT had not received prior chemotherapy (18.2% of patients had received prior docetaxel chemotherapy). All patients in the IMPACT trial were either ECOG 0 or 1, and over 80% of patients were ECOG 0.[9]

Thus, the benefit of using sipuleucel-T in men with mCRPC and a shorter life expectancy appears to be limited. Patients with very symptomatic disease and a poor performance status would be unlikely to gain a significant survival benefit from the use of sipuleucel-T and should be directed towards alternative options.

Index Patient 5

Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy

As patients with prostate cancer receive hormonal therapy earlier in the course of the disease (frequently for non-metastatic disease), they may actually develop castration-resistant disease (based on serologic progression) with non-metastatic or asymptomatic metastatic disease. Thus, additional agents, including docetaxel chemotherapy may be administered earlier in the course of metastatic disease. These trends have resulted in a population of mCRPC patients who have completed docetaxel and may continue to be asymptomatic or minimally-symptomatic with an excellent performance status. While such patients may be healthy enough to receive a number of subsequent therapies, a focus of therapy should also be to maintain their excellent performance status without significant toxicity from additional therapy. It is in this context that providers should choose from a number of additional therapies to offer to this patient population.

Guideline Statement 16.

Clinicians should offer treatment with abiraterone plus prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who received prior docetaxel chemotherapy. If the patient received abiraterone plus prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide. (Standard; Evidence Level Grade A [abiraterone] / B [cabazitaxel] / A [enzalutamide])

The trend over the past six to seven years has been to use docetaxel earlier in the course of treatment for a patient with castration-resistant disease, perhaps in those with minimal symptoms or even the asymptomatic patient with evidence of serologic or radiographic progression. The result is that many patients who have received and failed docetaxel have an excellent performance status and some may remain asymptomatic from their disease. Thus, the risk/benefit ratio of subsequent therapy and the desire to maintain an excellent QOL should certainly be of primary concern when selecting additional therapies post-docetaxel. In this light, abiraterone plus prednisone and enzalutamide appear to provide clinical benefit equivalent to (if not superior to) additional intravenous chemotherapy with an agent such as cabazitaxel. Abiraterone plus prednisone and enzalutamide have significantly less acute toxicity and no apparent cumulative toxicity in patients receiving these agents for prolonged periods. This is in contradistinction to cabazitaxel, which may show cumulative bone marrow toxicity (manifested by pancytopenia) and also cumulative neurotoxicity, particularly in patients with some underlying peripheral neuropathy from their prior docetaxel. Both abiraterone plus prednisone and enzalutamide represent excellent treatment options for such a patient. While there have been no randomized trials comparing these agents and little information exists regarding appropriate sequencing of these drugs, patients may have prolonged responses to either or both of these agents. With the FDA's expansion of the label indication for abiraterone plus prednisone to the pre-chemotherapy setting based on the results of a phase III clinical trial,[23] patients will have increasingly already been exposed to and progressed on abiraterone plus prednisone by the time they reach the post-docetaxel setting, making enzalutamide a preferable option compared to cabazitaxel.

Abiraterone: In a phase III trial (COU-AA-301), 1,195 patients who had failed docetaxel received 1,000 mg abiraterone plus prednisone or placebo. At a median of 12.8 months, OS and PFS favored the abiraterone plus prednisone cohort (14.8 months v.10.9 months; hazard ratio, 0.65; P<0.001 and 5.6 months v. 3.6 months; P<0.001, respectively).[7] As previously noted, abiraterone plus prednisone was well tolerated during clinical trial but did show an increase in adverse events and specifically those side effects related to mineralocorticoid excess.

Cabazitaxel: Cabazitaxel is another tubulin-binding taxane chosen for clinical development because of preclinical activity in tumor models resistant to other taxanes. An open-label, randomized phase III trial compared cabazitaxel at 25 mg/M^2 intravenously with oral prednisone versus mitoxantrone at 12 mg/M^2 intravenously with the same dose of prednisone, both administered on an every three week basis.[10] In this trial 755 patients who had received prior docetaxel were randomized, and the group receiving cabazitaxel demonstrated improved OS (15.1 months v 12.7 months) and improved PFS (2.8 months v 1.4 months). Cabazitaxel resulted in more-clinically-significant diarrhea, but its primary toxicity is hematologic with 82% of patients developing grade 3 or 4 neutropenia, 8% developing febrile neutropenia and 5% resulting in death. The FDA label indication for this drug recommends prophylactic neutrophil growth factor support in those patients most susceptible to neutropenia, including older individuals and those with significant prior radiotherapy. Because of the need for intravenous administration, the more modest clinical benefit and the higher rates of significant toxicity, cabazitaxel is ranked below abiraterone plus prednisone and enzalutamide for this group of patients.

Enzalutamide: Phase I/II data showed serologic and radiographic responses in both chemo-naïve patients as well as those who had received prior chemotherapy.[36] The subsequent double-blind, placebo-controlled AFFIRM phase III trial was performed in 1,199 patients who had received prior docetaxel therapy.[6] Patients received either enzalutamide 160 mg/day orally or placebo, and OS, the primary endpoint, favored enzalutamide (18.4 months v 13.6 months). There was also statistical superiority of enzalutamide for all secondary endpoints, including percentage of patients with 50% PSA reduction, soft-tissue response rate, QOL response rate, time to PSA progression, radiographic PFS and time to first SRE. Toxicity from enzalutamide was related primarily to fatigue, diarrhea and hot flashes, although 5 of 800 patients receiving the drug developed seizure activity. This drug was approved by the FDA in August of 2012 and represents another highly active oral agent with minimal toxicity available to these patients.

Guideline Statement 17.

Clinicians may offer ketoconazole plus steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone plus prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)

A number of clinical trials have established the efficacy and toxicity of high-dose ketoconazole in this setting,[30, 37-42] with as many as 50% of patients showing a > 50% drop in PSA, fewer bidimensionally measurable disease responses and a median time to progression of five to eight months. One study has suggested that 1) prior response to an antiandrogen; 2) pre-treatment PSA doubling time; and 3) extent of disease may be associated with the likelihood of clinical response to this therapy.[39] Although ketoconazole likely has a lower response rate, a shorter time to progression and higher incidence of significant toxicity than abiraterone plus prednisone, it remains a viable alternative for patients unable to obtain abiraterone plus prednisone.

Guideline Statement 18.

Clinicians may offer retreatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)

Much of the benefit of docetaxel in the mCRPC patient is seen in improvement of survival and QOL. However, prolonged, continuous therapy with docetaxel can result in cumulative, progressive, non-hematologic toxicity (e.g. neuropathy) that may more than counterbalance any potential serologic, radiographic or symptomatic benefit the patient may be receiving from the drug. In an effort to prolong the overall period of disease control with docetaxel, to allow reversible side effects to improve and to maximize overall QOL by spending as much time off chemotherapy as possible, the use of intermittent therapy with built-in drug holidays has become a common practice. Non-randomized data[43-46] as well as one randomized trial[47] suggests that a minority of patients may retain sensitivity to the drug with multiple discontinuous periods of administration. It is apparent that those drug holidays may last, on average, four to five months and that subsequent non-treatment periods might also last a number of months. It is logical to assume that patients with the most dramatic clinical benefit from prior docetaxel and with a more prolonged period off therapy prior to reinstitution are more likely to benefit from additional treatment with the same drug. Patients with these characteristics and who have recovered from prior toxicity may be considered for a re-trial of docetaxel before this drug is discarded from the armamentarium.

Guideline Statement 19.

Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

During the course of cancer treatment, bone marrow can become infiltrated by the cancer. Chemotherapeutic agents, such as docetaxel, can suppress bone marrow function while being used to extend survival and improve quality of life. Radium-223 was shown to be an

effective therapy in the previously discussed Parker et al. study[11] in which 57% of patients had previously received chemotherapy. As with other treatments, such as EBRT, side effects can include anemia and thrombocytopenia. Those patients who have previously received chemotherapy are at greater risk for such side effects compared to chemotherapy-naive patients.

Index Patient 6

Symptomatic, mCRPC with poor performance status and prior docetaxel chemotherapy

The American Society of Clinical Oncology (ASCO) has posted recommendations regarding treatment for patients with advanced solid tumors; particularly in the last months of life. ASCO advocates for an increasing emphasis on a patient's QOL and concentrates on symptom management. Treatment given in the last months of life may delay access to end of life care, increase costs and add unnecessary symptom management. Patients with poor performance status (ECOG 3 or 4) should not be offered further treatment (http://www.choosingwisely.org/doctor-patient-lists/american-society-of-clinical-oncology/).

Guideline Statement 20.

Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid or radionuclide therapy. (Expert Opinion)

Palliative care 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. Advanced prostate cancer can be debilitating with bone pain, fatigue and weight loss. Palliative radiotherapy can be an option for controlling bone pain in some patients. An increasing dependence upon others and a feeling of losing control can contribute to anxiety and depression. Other symptoms include urinary outflow obstruction, weakness secondary to spinal cord compression, lymphedema and anemia. Evaluation and treatment should be comprehensive and patient centered, focusing on the goals of the individual patient as well as the patient's family. Comprehensive palliative care often requires a multidisciplinary approach where various providers of differing expertise assess and treat the complex needs of the advanced disease prostate cancer patient.[48,49]

Abiraterone: Abiraterone is for patients who have CRPC that is resistant to medical or surgical treatments and who have received prior docetaxel chemotherapy. Method of action and dosing information are previously referenced.

Enzalutamide: Enzalutamide is indicated for the treatment of patients with mCRPC who have previously received docetaxel. The previously discussed AFFIRM study found that enzalutamide significantly prolonged the survival of men with mCRPC after chemotherapy. Method of action and dosing information are previously referenced.

Ketoconazole: Ketoconazole provides an available but fairly toxic treatment plan for patients with mCRPC who have received prior docetaxel chemotherapy with poor performance status. Method of action and dosing information are previously referenced.

Radionuclide Therapy: One example of a Phase III randomized clinical trial of radioactive samarium-153 (^{153}Sm) lexidronam versus nonradioactive ^{153}Sm-lexidronam for palliation of bone pain in patients with CRPC is by Sartor (2004).[49] A total of 152 men with painful bone metastases were enrolled in this prospective, randomized, double-blind trial. Patients were randomized (2:1) to the radioactive ^{153}Sm-lexidronam agent. Inclusion criteria were advanced prostate cancer progressing despite medical or surgical orchiectomy, a positive bone scan, pain scores of greater than 30mm on a 100mm visual analog scale or the use of opioid analgesics in daily doses equivalent to 60mg oral morphine, a Karnofsky performance status of less than 50% and life expectancy of greater than four months. Exclusion criteria were hormonal treatment initiated within eight weeks of dosing or radiotherapy administered within six weeks, pathologic fractures, spinal cord compression, prior hemibody irradiation, inadequate hematological, renal or liver function, allergies to phosphate compounds and prior exposure to radiopharmaceutical agents or bisphosphonates within six months of dosing. Patients completed pain and analgesic diaries twice daily. Blinded medications were given intravenously; the study was unblinded after four weeks when 28 of 52 placebo patients had not achieved satisfactory pain relief by week four; 22 of 28 chose to receive open label treatment with radioactive ^{153}Sm-lexidronam. The authors concluded that 1 mCi/kg ^{153}Sm-lexidronam is safe and effective for palliation of painful bone metastases in patients with hormone-refractory prostate cancer. Side effects included mild bone marrow suppression. The mean nadir white blood cell and platelet count (three to four weeks after treatment) was 3,800/μL and 127,000/μL, respectively. Counts recovered to baseline after approximately eight weeks. No grade 4 decreases in either platelets or white bloods cells were documented.

Multiple non-randomized trials have been done with Samarium-153 alone[50,51] with unclear adverse events and outcomes. Other studies included Samarium-153 with docetaxel;[52,53] these studies were also unclear in outcomes or adverse events. Studies looking at radium-223 have focused on those patients with good performance status, and there is no data indicating an advantage over standard radiopharmaceuticals in this patient population.

Guideline Statement 21.

Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with

poor performance status who received prior docetaxel chemotherapy. (Expert Opinion)

There is insufficient evidence demonstrating a benefit in this patient population. The potential for harm greatly outweighs the potential benefit, so these treatments should not be offered.

Guideline Statements on Bone Health (not specific to any one index patient)

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 the 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.[54,55] Finally, in patients with advanced disease, bones are the most common site of metastatic disease, with as many as 70% of patients at some point in their course demonstrating evidence of disease in this site.

Guideline Statement 22.

Clinicians should offer preventative treatment (e.g. supplemental calcium, vitamin D) for fractures and skeletal related events to CRPC patients. (Recommendation; Evidence Level Grade C)

Published data on the use of supplemental calcium and vitamin D to minimize bone mineral density loss in individuals on hormonal therapy with or without bony metastatic disease are confusing, and the discussion contentious. Part of the confusion arises from different populations of patients being studied (elderly patients without cancer, post-menopausal women, prostate cancer patients on ADT, etc.) as well as differences in the doses of the supplements and the inability to model vitamin D's physiologic effect on intestinal absorption of calcium in the laboratory setting.

Vitamin D: A meta-analysis of randomized controlled trials in over 9,000 patients 60 years of age or older has reported a reduction in the relative risk of hip fracture of 26% (compared to calcium alone or placebo) and of non-vertebral fractures by 23%, although these reductions were only observed with higher doses of vitamin D (700-800 IU/day).[56] There was no benefit observed at 400 IU/day, a dose commonly incorporated into multivitamin preparations. In another study summarizing the results of 12 clinical trials of calcium and vitamin D supplementation in males undergoing ADT for prostate cancer, doses of vitamin D in the 200-500 IU/day range were inadequate to prevent loss of bone mineral density.[57]

Calcium: Since hypocalcemia requiring dose modification or abandonment is a not-uncommon side effect of both zoledronic acid and denosumab, it seems reasonable to offer supplemental calcium to individuals receiving these drugs in an effort to maintain supportive therapy. However, it would appear that calcium supplementation alone (500-1,000 mg/day) cannot prevent bone mineral density loss from ADT.[57] Also, calcium supplementation may not be innocuous, as epidemiologic studies have suggested a relationship between calcium intake and the risk of subsequent cardiovascular disease[58,59] and prostate cancer risk including fatal prostate cancer, though conflicting data exist.[60,61]

With these caveats, it is impossible to make firm recommendations regarding the use of supplemental calcium and vitamin D in prostate cancer patients who will experience bone mineral density loss from long-term ADT. Practitioners who choose to recommend these supplements should be aware of the potential risks and benefits.

Guideline Statement 23.

Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for mCRPC patients with bony metastases. (Option; Evidence Level Grade C)

Denosumab: RANK –ligand and its inhibitors are important molecules involved in bone turnover. RANKL is an important driver of osteoclast function and survival. Denosumab is a human monoclonal antibody directed against RANKL and inhibits osteoclast-mediated bone destruction. In patients with non-metastatic disease receiving ADT, denosumab has been shown to actually increase bone mineral density at the total hip, femoral neck and lumbar spine and decrease the incidence of vertebral fractures.[62] In a subsequent randomized trial in over 1,900 patients with mCRPC, subcutaneous denosumab demonstrated a longer time to first SRE compared to intravenous zoledronic acid given on an every four-week schedule (20.7 months v 17.1 months).[63] Denosumab resulted in more significant hypocalcemia (13% of patients v. 6%). For this reason when prescribing denosumab it is recommended to include supplemental calcium and to monitor serum calcium level. While denosumab does not need to be dose adjusted based on serum creatinine, 22% of patients receiving zoledronic acid required baseline dose adjustment based on renal function, and an additional 15% required additional dose modifications due to serum creatinine while on study. Osteonecrosis of the jaw was uncommon in both arms (2% denosumab, 1% zoledronic acid). Based on these data, both denosumab and zoledronic acid can be considered options, with denosumab providing slightly superior efficacy results in a head-to-head comparison, and therefore is listed as the first option.

Zoledronic acid: Bisphosphonates as a class are potent inhibitors of bone resorption, and several drugs in this class have previously been shown to decrease the incidence of skeletal complications with breast cancer and multiple myeloma. Zoledronic acid is the only bisphosphonate to demonstrate a beneficial effect in

patients with mCRPC. In a phase III randomized trial[64] 4 mg of zoledronic acid given intravenously every three weeks: 1) decreased the incidence of SREs by 36%, and 2) longer therapy (up to 24 months) appears to confer continued benefit, even in patients who have experienced one SRE, when compared to placebo. The toxicity of this therapy includes a small incidence of osteonecrosis of the jaw, hypocalcemia and nephrotoxicity. These latter two mandate that serum creatinine and serum calcium be obtained prior to each dose with appropriate dose modifications for abnormal results.

Radionuclide Therapy: Intravenous radionuclides have been developed in an attempt to palliate patients with painful bony metastases. Initially strontium-89 was developed and provided short-term improvement in pain in a minority of patients but at the expense of moderate to severe bone marrow toxicity, likely related to its prolonged half-life.[65-67] Samarium-153 has been shown in two randomized trials to provide palliation to patients with painful bony metastases and to have less severe and more transient hematologic toxicity, likely related to its shorter half-life,[68,69] which also results in the possibility of giving multiple doses to patients safely.[70] The toxicity profile alone would result in the selection of samarium-153 over strontium-89 in this group of patients.

Future Directions

Over the past 15 years there has been unparalleled scientific progress and investment in drug development for patients with CRPC. As a direct result of these studies, several lines of systemic therapies have been FDA approved for use in CRPC on grounds of pain palliation, minimizing disease adverse effects, and prolonging survival.

Future Research. The impact on survival in mCRPC from each of these individual agents thus far continues to be modest, being measured only in months. To further impact outcomes therapy, development in this stage of disease must focus on the totality of disease biology integrating a comprehensive molecular understanding of castration resistance and investigating mechanisms of resistance to current therapies so as to better guide future treatment development. Continued investments in discovery, investigation and validation of important new candidate targets is needed.

One of the glaring deficiencies in prostate cancer drug development, by comparison to several other solid tumors, has been the lack of predictive biomarkers to help better personalize therapy. This is especially important if we are to optimize risk/benefit, particularly given that a significant percentage of patients do not benefit or have small benefits from current FDA approved agents.

In addition to the continued investigation of new agents in the mCRPC population, it is critical that we prospectively define the optimal sequence of approved treatments in order to guide proper use taking into account efficacy and cost-effectiveness, particularly for agents that target similar pathways. Furthermore, maximizing the anti-tumor effect by investigating scientifically rational combinations should be an area of high priority.

Over the past decade there have been considerable advances in our biologic understanding of mCRPC that have led to an explosion of novel treatments. Unfortunately, mCRPC remains a fatal disease. Hence, research to maximize the efficacy of ADT with the use of even more effective agents and investigating alternative combination strategies in well-designed and supported clinical trials is critical.

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CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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Amendment COI

Amendment panels consist of small subsets of the original panel with additional panelists included as needed based on subject matter expertise. COI disclosures for amendment panelists are listed below:

2014 Amendment:

Scientific Study or Trial: Bruce Roth, Oncogenix, Exelixis, Medivation, Argos; **Adam Kibel,** Sanofi Aventis

Consultant/Advisor: Adam Kibel, Dendreon, Sanofi Aventis

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2015 Amendment:

Consultant/Advisor: Michael S. Cookson, PersonalizeDx

Meeting Participant or Lecturer: Michael S. Cookson, Janssen

Scientific Study or Trial: Bruce Roth, Oncogenix, Exelixis, Medivation, Argos ; **William Lowrance,** Myriad Genetics, GenomeDx, Argos

2018 Amendment:

Investment Interest: William Lowrance, StreamDx

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DISCLAIMER

The development of the original version of this Castration-Resistant Prostate Cancer Guideline was initiated in 2011 by a multi-disciplinary panel assembled by the Practice Guidelines Committee of the American Urological Association Education and Research, Inc. (AUA). This amended Castration-Resistant Cancer Guideline was drafted in 2018 by a subset of the original Castration-Resistant Prostate Cancer Guideline panel with additional participation from outside content experts. This amendment updates the original guideline document to reflect literature released following the original publication.

The mission of the original and amendment panels was to develop clinical guideline recommendations based on an in-depth evidence report of the peer-reviewed literature. The recommendations are based on evidence strength, or where evidence is not available, on Delphi-modification consensus statements. The purpose of each guideline is to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of castration-resistant prostate cancer. 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.

Funding of the original and amendment panels was provided by the AUA. Panel members receive no remuneration for their work. Panel members' potential conflicts of interest are subject to rigorous and on-going review during the development of the original guideline, and amendment panel members are screened for conflicts throughout the amendment process.

As medical knowledge expands and technology advances, AUA guidelines are subject to change. Evidence-based guidelines statements are not absolute mandates but thoroughly considered strategies for best practice 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. Similarly, conformance with any clinical guideline cannot assure a successful outcome. These guidelines and best practice statements are not intended to provide legal advice.

The guideline text may include information or recommendations about certain drug or device use (‘off label‘) that are not approved by the 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 understand and carefully follow all available prescribing information about indications, contraindications, precautions and warnings.

Although guidelines are intended to encourage best practices and to reflect available technologies with sufficient data as of the date of close of the literature review, guidelines are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies, pharmaceuticals or management practices, including both those that are FDA-approved, or those which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard emerging technologies or management techniques not addressed by this guideline as manifestly experimental or investigational. These emerging technologies or techniques may simply be too new to be included or fully incorporated in the panel's evidence-based evaluation at the time the guideline is developed.