Castration-Resistant Prostate Cancer: AUA Guideline

Michael S. Cookson, Bruce J. Roth, Philipp Dahm, Christine Engstrom, Stephen J. Freedland, Maha Hussain, Daniel W. Lin, William T. Lowrance, Mohammad Hassan Murad, William K. Oh, David F. Penson and Adam S. Kibel

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Purpose: This Guideline is intended to provide a rational basis for the management of patients with castration-resistant prostate cancer based on currently available published data.

Materials and Methods: 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 search strategy was developed and executed by reference librarians and methodologists to create an evidence report limited to English-language, published peer-reviewed literature. This review yielded 303 articles published from 1996 through 2013 that were used to form a majority of the guideline statements. Clinical Principles and Expert Opinions were used for guideline statements lacking sufficient evidence-based data.

Results: Guideline statements were created to inform clinicians on the appropriate use of observation, androgen-deprivation and antiandrogen therapy, androgen synthesis inhibitors, immunotherapy, radionuclide therapy, systemic chemotherapy, palliative care and bone health. These were based on six index patients developed to represent the most common scenarios encountered in clinical practice.

Conclusions: As a direct result of the significant increase in FDA-approved therapeutic agents for use in patients with metastatic CRPC, clinicians are challenged with a multitude of treatment options and potential sequencing of these agents that, consequently, make clinical decision-making more complex. Given the rapidly evolving nature of this 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, patients’ preferences and personal goals should be considered when choosing management strategies.

Key Words: prostatic neoplasms, androgen antagonists, drug therapy, immunotherapy

INTRODUCTION

The purpose of this guideline is to provide direction to clinicians and patients regarding the management and treatment of castration-resistant prostate cancer. To assist in clinical decision-making, six index cases were developed representing the most common clinical scenarios that are encountered in clinical practice (see table).

METHODOLOGY

The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on various therapies for CRPC. Guideline
**BACKGROUND**

**Definition**
For the purpose of the guideline, CRPC was defined as a rising prostate specific antigen level and/or radiographic evidence of prostate cancer progression despite medical or surgical castration.

**Prevalence**
Prostate cancer is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among men. Approximately 240,000 new diagnoses of prostate cancer and over 28,000 deaths were estimated in the U.S. in 2012. While most advanced prostate cancer patients respond initially to androgen deprivation therapy, they ultimately progress despite castration on average between one and three years after initiation of therapy.

**Changing Treatment Paradigm**
The treatment of men with mCRPC has dramatically changed in the last decade. Prior to 2004, once patients failed primary ADT, treatments were administered solely for palliation. Landmark articles by Tannock et al and Petrylak et al demonstrated that docetaxel improved survival for these patients with mCRPC. Since the approval of docetaxel, four additional agents (enzalutamide, abiraterone, sipuleucel-T and cabazitaxel) that show a survival benefit have been FDA-approved on the basis of randomized clinical trials. These agents have been tested in multiple “disease states” of CRPC to determine if or when patients might benefit from each treatment.
GUIDELINE STATEMENTS

Index Patient 1
1. Clinicians should recommend observation with continued androgen deprivation. (Recommendation; Evidence Level Grade C)

   Since all agents have potential side effects, and no treatment has been shown to extend survival or demonstrate a clinically meaningful delay in the development of metastasis, we must first do no harm. As such, it is the Panel’s judgment that no treatment (i.e. observation) other than continued ADT be the recommended treatment based upon the lack of any data to refute this recommendation. Patients should be encouraged to enter clinical trials, when available.

2. Clinicians may offer treatment with first-generation antiandrogens (flutamide, bicalutamide and nilutamide) or first-generation androgen synthesis inhibitors (ketoconazole + steroid) to select patients with non-metastatic CRPC who are unwilling to accept observation. (Option; Evidence Level Grade C)

   While it is the Panel’s judgment that observation is the most appropriate treatment for this patient population, some patients in this setting may be uncomfortable with treatment with systematic ADT alone and may wish to initiate additional treatment despite the lack of good evidence with regards to the benefits and harms in this setting.

Antiandrogens. Though first-line antiandrogens (flutamide, bicalutamide and nilutamide) are commonly used, these agents can be associated with side effects, including gastrointestinal upset and liver toxicity. Though some small single-arm non-randomized studies suggest a PSA decline, the potential benefit appears modest with PSA declines greater than 50% occurring typically in 20% to 40%
of men with a median duration of only several months. In addition, antiandrogen withdrawal has been used as an option in this setting. There are no randomized studies of either antiandrogens or antiandrogen withdrawal compared to observation; as such, there is a lack of data suggesting any meaningful clinical benefit.

**Androgen synthesis inhibitors (ketoconazole).** 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. There are multiple single-arm studies that show PSA response rates (greater than 50% decline in PSA) of 30% to 60% with typical responses around 50%.11–17

| Option; Evidence Level Grade C |

There are no data to support use of these agents in this patient population. The combination of no known benefit with known and potentially serious harms results in a recommendation not to use these agents.

**Index Patient 2**

4. Clinicians should offer abiraterone+prednisone, 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)/B (docetaxel)/B (sipuleucel-T)]

Docetaxel chemotherapy and sipuleucel-T immunotherapy are currently the only agents that have demonstrated a survival advantage, while abiraterone+prednisone has demonstrated radiographic progression-free survival benefits. All three have an FDA indication for use in men with mCRPC who have not yet received docetaxel chemotherapy.

**Abiraterone.** Abiraterone is an irreversible inhibitor of the hydroxylase and lyase activities of CYP17A. Prior to docetaxel chemotherapy, abiraterone+prednisone demonstrated an improvement in radiographic PFS and a trend toward improvement in overall survival in the COU-AA-302 study.18 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 prevent these treatment-related increases in adrenocorticotropic hormone and attendant side effects.

**Docetaxel.** Docetaxel is a potent inhibitor of microtubule assembly and disassembly. In a randomized trial of men with mCRPC (TAX-327), patients who received docetaxel+prednisone every three weeks had significantly better survival than those receiving mitoxantrone.3 While this study provides strong evidence to support the use of docetaxel+prednisone in men with mCRPC, there are two important caveats. First, this study did include many patients with symptomatic mCRPC (Index Patient 3). Second, 26% of patients in the docetaxel+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. 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 immunotherapy is an FDA-approved agent in this setting based upon the results of the IMPACT trial.19 In this randomized double-blind placebo controlled clinical trial, men with asymptomatic or minimally symptomatic mCRPC and good functional status treated with sipuleucel-T, as compared to placebo, had a significant reduction in the risk of death. It is worth noting that patients receiving sipuleucel-T therapy rarely (less than 10%) exhibit a clinical, serologic or radiographic response; as such, patients should be counseled appropriately not to expect to see a decline in PSA or reduction in radiological volume of disease when undergoing this treatment.

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 considered in light of other considerations, including convenience of administration.

5. Clinicians may offer first-generation antiandrogen therapy 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 antiandrogen agents, such as bicalutamide, nilutamide or flutamide, 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 these options in the setting of asymptomatic or minimally symptomatic prostate cancer are limited and generally of lesser strength than the standard treatments. Some have suggested that the removal of antiandrogen therapy may have a beneficial effect on mCRPC. The majority of studies supporting this approach are observational, and the single randomized clinical trial addressing this issue failed to show any survival benefit associated with antiandrogen withdrawal.\(^\text{20}\)

Finally, some patients may not wish to pursue any therapy, waiting for the onset of symptoms to pursue treatment (if they are to ever elect treatment at all). Given current data in this patient population, this approach is a reasonable option.

**Index Patient 3**

**6. Clinicians should offer docetaxel to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade B)**

**Docetaxel.** As previously noted, high-quality evidence supports the use of first-line docetaxel every three weeks with daily prednisone in symptomatic mCRPC.\(^\text{3,4}\) Bone pain responses were more significant in docetaxel patients (35\% vs. 22\%, \(p = 0.08\)) as were improvements in quality of life compared to the mitoxantrone group.

**7. Clinicians may offer abiraterone+prednisone to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)**

**Abiraterone+prednisone.** In the previously discussed COU-AA-302 study, the Independent Data Monitoring Committee unanimously recommended unblinding based on a planned interim analysis of radiographic PFS, OS and clinical benefit. At 22 months of follow-up, neither median radiographic PFS nor OS for the abiraterone arm had been reached, but the hazard ratio for radiographic PFS was reported as 0.53 (95\% CI: 0.45, 0.62) that was statistically significant (\(p < 0.001\)). OS was improved with abiraterone+prednisone (median survival not yet reached vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95\% CI, 0.61 to 0.93; \(p = 0.01\)) but did not cross the efficacy boundary.\(^\text{18}\) 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 this patient population regardless of symptoms; therefore, it is appropriate for Index Patient 3.

**8. Clinicians may offer ketoconazole+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-naïve mCPRC. Ketoconazole has substantial treatment-related side effects that have prompted the development of more potent CYP17A inhibitors, such as abiraterone.

**Mitoxantrone.** Mitoxantrone, a microtubule inhibitor, has not shown a survival benefit compared to docetaxel-based chemotherapy regimens in mCRPC as previously discussed.\(^\text{15}\) Mitoxantrone is primarily utilized in symptomatic mCRPC patients with poor performance status (ie 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 randomized study.\(^\text{21}\)

**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.\(^\text{22,23}\) The risk of bone marrow suppression, which might influence the ability to administer systemic chemotherapy agents, should be considered before initiation of radionuclide therapy.

**9. 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. The major mechanism of action is as an alkylating agent that has not shown significant OS advantages. Given the significant toxicity with estramustine, its use cannot be encouraged.\(^\text{5}\)

**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.\(^\text{19}\)
patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)

In the previously discussed COU-AA-302 study, OS did not meet the pre-specified boundary for significance at the early point of unblinding. Thus, though survival trend is better with abiraterone+prednisone, it remains unclear if abiraterone+prednisone improves OS. Nevertheless, the FDA approved the label for use of abiraterone+prednisone in mCRPC independent of docetaxel treatment. Notably, COU-AA-302 was administered only in good performance status patients, but it is the Panel’s opinion that abiraterone+prednisone would be a reasonable alternative to chemotherapy for patients even with a poor performance status.

11. Clinicians may offer treatment with ketoconazole+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+prednisone. (Option; Evidence Level Grade C)

Ketoconazole. Ketoconazole has been demonstrated to have anti-cancer effects in the setting of mCRPC and could be a viable alternative, in particular if abiraterone+prednisone is unavailable.

Radionuclide therapy. Samarium-153 and strontium-89 have not shown a survival benefit but may offer palliative benefit in patients symptomatic with bone pain.

12. 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 cancer related and non-prostate cancer related causes. The latter patient may benefit from treatment.

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.

Mitoxantrone. Mitoxantrone was approved based on two randomized trials that demonstrated a palliative benefit in symptomatic mCRPC. 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. If the poor performance status is not related to cancer progression, then systemic chemotherapy of any kind is not recommended.

13. 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. Sipuleucel-T appears to benefit patients with a lower disease burden and better performance status. 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 toward alternative options.

Index Patient 5

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

Abiraterone+prednisone and enzalutamide have clinical benefit and may be administered with significantly less acute toxicity and no apparent cumulative toxicity as compared to approved chemotherapy in this clinical scenario. This is in contradistinction to cabazitaxel that may show cumulative bone marrow toxicity (manifested by pancytopenia), but also cumulative neurotoxicity, particularly in patients with some underlying peripheral neuropathy from their prior docetaxel.

Abiraterone+prednisone. In a phase III trial (COU-AA-301), patients who had failed docetaxel received abiraterone+prednisone or placebo. At a median of 12.8 months, OS and PFS favored the abiraterone+prednisone cohort. As previously noted, abiraterone+prednisone was well tolerated during clinical trial but did show an increase in adverse events, specifically those side effects related to mineralocorticoid excess.
**CABAZITAXEL.** Cabazitaxel is a tubulin-binding taxane chosen for clinical development because of pre-clinical activity in tumor models resistant to other taxanes. An open-label, randomized phase III trial compared cabazitaxel with oral prednisone vs mitoxantrone with the same dose of prednisone, both administered on an every three week basis.\(^{26}\) In this trial, patients who had received prior docetaxel were randomized, and the group receiving cabazitaxel demonstrated improved OS and PFS. Cabazitaxel resulted in more clinically significant diarrhea, but its primary toxicity is hematological, with 82% of patients developing grade 3 or 4 neutropenia, 8% developing febrile neutropenia and 5% deaths. 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+prednisone and enzalutamide for this group of patients.

**Enzalutamide.** Enzalutamide is a novel androgen-receptor signaling inhibitor. The double-blind, placebo controlled phase III AFFIRM trial was performed in men who had received prior docetaxel therapy.\(^{27}\) Patients received either enzalutamide or placebo, and OS, the primary end point, favored enzalutamide. 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 and represents another highly active oral agent with minimal toxicity available to these patients.

15. Clinicians may offer ketoconazole+steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone+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,\(^{28}\) with as many as 50% of patients showing greater than 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 anti-androgen; 2) pretreatment PSA doubling time; and 3) extent of disease may be associated with the likelihood of clinical response to this therapy.\(^{28}\) Although ketoconazole likely has a lower response rate, a shorter time to progression and higher incidence of significant toxicity than abiraterone+prednisone, it remains a viable alternative for patients unable to obtain abiraterone+prednisone.

16. Clinicians may offer re-treatment 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)

In an effort to prolong the overall period of disease control with docetaxel, to allow reversible side-effects to improve and to maximize 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 as well as one randomized trial\(^{29}\) suggest 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 subsequent non-treatment periods might also last a number of months. Patients with these characteristics and who have recovered from prior toxicity may be considered for a re-trial of docetaxel.

**INDEX PATIENT 6**

17. 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+prednisone, enzalutamide, ketoconazole+steroid or radiotherapy. (Expert Opinion)

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.

18. 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**

Several factors conspire to place the average patient with metastatic prostate at a higher risk of bone complications. First, the median age of onset of the disease is in the late 60’s, meaning that the average patient with metastatic disease may be in his 70’s (or beyond), clearly a population at risk of physio-
logical, age-related decreases in bone mineral density. Secondly, ADT, a primary therapeutic intervention in patients with recurrent disease, 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.30,31 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.

19. 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)

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).32 There was no benefit observed at 400 IU/day, a dose commonly incorporated into multivitamin preparations.

Calcium
Supplemental calcium is recommended in general to help prevent bone loss. This is particularly important in men on either zoledronic acid or denosumab since hypocalcemia requiring dose modification or abandonment is a not-uncommon side effect. However, its use should be tempered by the fact that calcium supplementation alone (500–1,000 mg/day) cannot prevent bone mineral density loss from ADT.33 Also, calcium supplementation may not be innocuous, as epidemiologic studies have suggested a relationship between calcium intake and the risk of subsequent cardiovascular disease34,35 and prostate cancer risk including fatal prostate cancer, though conflicting data exist.36,37

20. 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
Denosumab is a human monoclonal antibody directed against RANKL and inhibits osteoclast-mediated bone destruction. In a randomized trial, patients with mCRPC treated with denosumab demonstrated a longer time to first skeletal-related event compared to zoledronic acid.38 Denosumab resulted in more significant hypocalcemia. For this reason, when prescribing denosumab, it is recommended to include supplemental calcium and monitor serum calcium level. Osteonecrosis of the jaw was uncommon in both arms. 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 are a class of potent inhibitors of bone resorption and have decreased the incidence of SREs. Zoledronic acid is the only bisphosphonate to demonstrate a beneficial effect in patients with mCRPC. In a phase III randomized trial,39 zoledronic acid decreased the incidence of SREs as compared to placebo. Furthermore, 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.

Radionuclide Therapy
Intravenous radionuclides have been developed in an attempt to palliate patients with painful bony metastases. 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 hematological toxicity, likely related to its shorter half-life40,41 that also results in the possibility of giving multiple doses to patients safely.42 The toxicity profile alone would result in the selection of samarium-153 over strontium-89 in this group of patients.

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. Consultant/Advisor: Michael S. Cookson, Spectrum (C), Myriad (C), US HIFU(C), Endo (C), GE Healthcare (C), Coviden (C); Stephen J. Freedland, Amgen (C), Medivation (C), Bayer (C), Mitomics (C), Astellas (C), AstraZeneca (C), Dendreon (C), Janssen (C), Glaxo Smith Kline (C) (Expired); Maha Hussain, Merck (C), Lilly (C), Exelexis (C), Johnson & Johnson (C); Adam S. Kibel, Dendreon (C), Myriad Genetics (C), National Cancer Institute (C), Sanofi-Aventis (C), Spectru (C); Daniel W. Lin, Caris Life Sciences (U), Dendreon Corporation (C), GenProbe (U), Myriad Genetics (C), Pfizer (C); William T. Lowrance, Myriad Genetics (C), Dendreon (C); William K. Oh, Active Biotech (C), Amgen (C), Astellas (C), Bayer (C), Bellicum Pharmaceuticals (C),...
Castration-Resistant Prostate Cancer

This document was written by the Castration-Resistant Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2011. The Practice Guidelines Committee of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists, and oncologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of Castration-Resistant Prostate Cancer. Funding of the committee was provided by the AUA. Committee members received no remuneration for their work. Each member of the committee provides an ongoing conflict of interest disclosure to the AUA. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (“off label”) that are not approved by the Food and Drug Administration, or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

REFERENCES


