Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II

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Abbreviations and Acronyms

ADT = Androgen deprivation therapy

AR = Androgen receptor

ART = Androgen receptor-targeted therapy

CRPC = Castration-resistance prostate cancer

CT = Computed tomography

mCRPC = Metastatic castration-resistance prostate cancer

MFS = Metastasis-free survival

MRI = Magnetic resonance imaging

nmCRPC = Non-metastatic castration-resistance prostate cancer

OS = Overall survival

PET = Positron emission tomography

PSA = Prostate specific antigen

PSADT = Prostate specific antigen doubling time

SRE = Skeletal-related event

Purpose: The summary presented herein represents Part II of the two-part series dedicated to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline discussing prognostic and treatment recommendations for patients with castration-resistant disease. Please refer to Part I for discussion of the management of patients with biochemical recurrence without metastatic disease after exhaustion of local treatment options as well as those with metastatic hormone-sensitive prostate cancer.

Results: The Advanced Prostate Cancer Panel created evidence- and consensus-based guideline statements to aid clinicians in the management of patients with advanced prostate cancer. Such statements are summarized in figure 1 and detailed herein.

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

Conclusions: This guideline attempts to improve a clinician's ability to treat patients diagnosed with advanced prostate cancer. Continued research and publication of high-quality evidence from future trials will be essential to improve the level of care for these patients.

Key Words: Prostate cancer, antiandrogens

CASTRATION-RESISTANT prostate cancer (CRPC), whether metastatic (mCRPC) or non-metastatic (nmCRPC), generally occurs in response to therapeutic pressure, specifically the use of androgen deprivation therapy (ADT). The exact mechanism of transition from hormone-sensitive to castration-resistant disease is still not fully understood, and some disease may be inherently resistant at presentation. However, it is clear that despite castrate levels of androgens, the androgen receptor (AR) remains active and continues to drive prostate cancer progression in most cancers.[1,2] As such, multiple agents have been developed that further decrease androgen production or block AR signaling in addition to standard ADT with luteinizing hormone-releasing hormone agonists or antagonists. It is hypothesized that there are additional biologic pathways that function independently of androgen signaling resulting in CRPC. With a greater understanding of tumor biology, there is hope for continued development of innovative treatment

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options that further improve survival for men with CRPC.

For a full description of the methodology used in the development of guideline statements, refer to the unabridged guideline available at www.auanet.org/guidelines.

GUIDELINE STATEMENTS

Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC)

Men with a rising prostate specific antigen (PSA) but no visible metastatic disease on conventional imaging despite medical or surgical castration represent a uniquely distinct disease state. The advent of improved imaging, including next generation positron emission tomography (PET)-computed tomography (CT) scanning, has allowed for the discovery of small volume metastases that were previously undetected with standard clinical imaging such as bone scans, CT, and magnetic resonance imaging (MRI). Nevertheless, there remains a subset of patients whose disease remains defined by biochemical PSA rise only. Until recently there have been no agents specifically FDA approved for the treatment of men with nmCRPC. However, three AR antagonists successfully prolonged metastasis-free survival (MFS), defined as the development of metastases or death from any cause, when compared with ADT plus placebo in men with nmCRPC.[3−5]

Prognosis. 19. In nmCRPC patients, clinicians should obtain serial PSA measurements at three- to six-month intervals, and calculate a PSA doubling time (PSADT) starting at the time of development of castration-resistance. (Clinical Principle)

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

Monitoring of men with nmCRPC should include serial measurements of PSA, whether patients are receiving ADT alone or ADT with an additional AR directed therapy (apalutamide, darolutamide, enzalutamide). PSADT should be calculated for men with a rising PSA in the setting of ongoing ADT (castration-resistance) as PSADT is useful in determining which men are at highest risk of developing metastatic lesions or dying from prostate cancer.[6] PSADT ≤10 months was used to identify the highest risk population for inclusion in the three trials that led to approval of the AR antagonists for men with nmCRPC and is recommended to consider when adding one of the medications to ADT in men with nmCRPC.[3−5]

In addition to monitoring PSA, routine use of conventional imaging should be integrated into monitoring the disease status of men with nmCRPC. The suggested interval of conventional imaging is 6 to 12 months, with the exact interval determined by the PSADT calculation, the development of symptoms, and patient/physician preference.

Treatment. 21. Clinicians should offer apalutamide, darolutamide, or enzalutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (Strong Recommendation; Evidence Level Grade A)

Apalutamide. In the double-blind, placebo-controlled, Phase 3 SPARTAN trial,[4] Smith et al. randomly assigned 1,207 men (2:1) to receive apalutamide or placebo. At the time of planned primary analysis,

NON-METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis	Treatment
Clinicians SHOULD	Clinicians SHOULD
Obtain serial PSA measurements at three to six month intervals and calculate PSA doubling time starting at time of development of castration-resistance	Offer apalutamide, darolutamide, or enzalutamide with continued ADT to patients at high risk for developing metastatic disease
	Clinicians MAY
Assess for development of metastatic disease using conventional imaging at intervals of six to twelve months	Recommend observation with continued ADT, particularly for those at lower risk for developing metastatic disease
	Clinicians SHOULD NOT
	Offer systemic chemotherapy or immunotherapy outside the context of a clinical trial

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis	Treatment (cont.)
Clinicians SHOULD	Clinicians SHOULD (cont.)
Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status	Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide
Assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy	Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy
Offer germline and somatic tumor genetic testing	Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high CRPC
Treatment	Clinicians MAY
Clinicians SHOULD	Offer sipuleucel-T to asymptomatic/minimally symptomatic patients
Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide	Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide
Consider prior treatment in sequencing agents and recommend therapy with an alternative mechanism of action	Offer platinum-based chemotherapy to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy who cannot use/obtain a PARP inhibitor
Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm	

Figure 1. Statement Summary

median MFS was 40.5 months in the apalutamide group compared to 16.2 months in the placebo group (HR=0.28; 95% CI 0.23−0.35; p <0.001). Median overall survival (OS) was not reached in the apalutamide group versus 39.0 months in the placebo group (HR=0.70; 95% CI 0.47−1.04; p=0.07).

Darolutamide. The randomized, double-blind, placebo-controlled, Phase 3 ARAMIS study[5] randomized 1,509 patients (2:1) to ADT with darolutamide or ADT with placebo. The median MFS was 40.4 months with darolutamide versus 18.4 months with placebo (HR=0.41; 95% CI 0.34−0.50; p <0.001). Median OS was not reached in either group.

Enzalutamide. The double-blind, placebo-controlled, Phase 3 PROSPER study[3] randomized 1,401 patients (2:1) to enzalutamide or placebo. Both arms continued ADT. 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 36.6 months in the enzalutamide arm compared to 14.7 months in the placebo group (HR=0.29; 95% CI 0.24−0.35; p <0.001). Following completion of the systematic review for this guideline, additional data were released on OS as of October 2019. The median OS was 67.0 months in the enzalutamide group and 56.3 months in the placebo group. Treatment with enzalutamide plus ADT was associated with a 27% lower risk of death versus placebo plus ADT (HR=0.73; 95% CI 0.61−0.89; p=0.001).[7]

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

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

It is the Panel's judgment that observation with continued ADT is recommended for patients with a PSADT >10 months. These patients have a lower risk of developing metastatic disease than patients with a PSADT ≤10 months.[8]

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

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

The treatment of men with mCRPC has dramatically changed over the past decade. Prior to 2004, once primary androgen deprivation failed to control the disease, treatments were administered solely for palliation. Landmark studies by Tannock et al. and Petrylak et al. demonstrated that docetaxel improved survival and quality of life for such patients with mCRPC.[9,10] Since the approval of docetaxel, multiple additional agents that show a survival benefit have been FDA approved on the basis of randomized controlled trials.[1−15] These agents have been tested in multiple "disease states" of mCRPC, both before and after docetaxel chemotherapy, to determine when patients might benefit from each treatment.

Prognosis. 24. In mCRPC patients, clinicians should obtain baseline labs (eg, PSA, testosterone, lactate dehydrogenase, hemoglobin, alkaline phosphatase level) and review location of metastatic disease (bone, lymph node, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision making. (Clinical Principle)

There are established laboratory and imaging characteristics known to be associated with prognosis among men with mCRPC. Known laboratory risk-factors associated with increasing risk of mortality include elevated lactate dehydrogenase, testosterone <20-50 ng/dL, higher PSA, and shorter PSADT.[16−20] There are established imaging findings also known to be associated with increasing risk of mortality. Increasing burden of metastatic disease in the form of the number of metastatic sites is associated with increasing risk of overall mortality.[21] Additionally, there are known relationships between location of metastases and risk of mortality.[22] Specifically, visceral metastases are known to portend the highest risk of mortality (HR=1.76; 95% CI 1.34−2.32 versus lymph node) followed by bone metastases (HR=1.52; 95% CI 1.20−1.93 versus lymph node).[23]

25. In mCRPC patients, clinicians should assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy. (Expert Opinion)

It is recommended that men with mCRPC undergo conventional imaging at least annually owing to the fact that in the PREVAIL trial, radiographic progression without PSA progression occurred in 24.5% of mCRPC patients treated with enzalutamide prior to chemotherapy. This suggests that routine imaging can identify a significant portion of patients with radiographic progression who would otherwise not be identified.[24] The precise timing of imaging among men with mCRPC should be determined by

multiple factors including biochemical response to treatment, change in disease-related symptoms, and patient preference. Furthermore, clinicians should consider known differences in biochemical response to treatment among different therapies for mCRPC when determining the interval between imaging studies.

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

Germline mutations in genes involved in DNA damage repair have been identified in over 11.8% of men with metastatic prostate cancer.[25] Germline mutations have been found to portend poor prognosis among men with metastatic prostate cancer. Specifically, cancer-specific survival among men found to be harboring a BRCA2 mutation was found to be half of that among men without a defect in DNA damage repair (17.4 months versus 33.2 months, p=0.027).[26] Mutations in tumor suppressor genes have also been found to be associated with adverse outcomes among men with prostate cancer. Specifically, the presence of one or more mutations in tumor suppressor genes was found to be associated with increasing risk of death among men with metastatic disease.

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

Abiraterone Acetate. In the placebo-controlled, double-blind, phase 3 COU-AA-302 study,[27] Ryan et al. randomized 1,088 men with mCRPC who had not received prior chemotherapy to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Participants randomized to receive abiraterone acetate plus prednisone had statistically significant improvement in radiographic progression free survival (HR=0.53; 95% CI 0.45−0.62; p <0.001), as previously reported during interim analyses.[27] The final analysis of OS showed a statistically significant increase in patients treated with abiraterone acetate plus prednisone (HR=0.81; 95% CI 0.70−0.93; p=0.0033).[28]

In the COU-AA-301 trial,[12] de Bono et al. randomly assigned 1,195 patients who had previously received docetaxel (2:1) to receive prednisone with either abiraterone acetate or placebo. After a median follow-up of 12.8 months, OS was 14.8 months in the abiraterone acetate group compared to 10.9 months in the placebo group (HR=0.65; 95% CI 0.54−0.77; p <0.001).

Enzalutamide. In the double-blind, phase 3 PREVAIL study,[29] Beer et al. randomized 1,717 chemotherapy-naïve patients to receive either enzalutamide or placebo. The results showed that enzalutamide significantly decreased the risk of radiographic progression (HR=0.19; 95% CI 0.15−0.23; p <0.001) and death (29% reduction in the risk of death; HR =0.71; 95% CI 0.60−0.84; p <0.001).

In the phase 3, double blind AFFIRM study,[11] Scher et al. stratified 1,199 men with CRPC after chemotherapy (2:1) to receive enzalutamide or placebo. At the time of planned interim analysis, the median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR for death in the enzalutamide group=0.63; 95% CI 0.53−0.75; p <0.001).

Docetaxel. In the TAX-327 trial,[9] Tannock et al. randomized 1,006 men with mCRPC and good performance status to receive 5 mg prednisone twice daily and either docetaxel 75 mg/M^2 every three weeks, docetaxel 30 mg/M^2 weekly, or mitoxantrone 12 mg/M^2 weekly. Patients who received docetaxel plus prednisone every three weeks had significantly better survival than those receiving mitoxantrone (HR for death =0.76; 95% CI 0.62−0.94; p=0.009). Median survival in the docetaxel plus prednisone every three weeks group was 18.9 months compared to 16.5 months in the mitoxantrone group. Analysis at longer follow-up demonstrated the median survival advantage improved slightly to 19.2 months compared to 16.3 months for mitoxantrone (p=0.004).[30] No significant survival differences were noted between the weekly docetaxel plus prednisone group and the mitoxantrone group.

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

In the randomized double-blind placebo controlled IMPACT trial,[13] 512 men with asymptomatic or minimally-symptomatic mCRPC and good functional status were randomized (2:1) to receive either sipuleucel-T or placebo. Compared to placebo, sipuleucel-T was associated with a relative reduction of 22% in the risk of death (HR=0.78; 95% CI 0.61−0.98; p=0.03). Median survival in the sipuleucel-T arm was 25.8 months compared to 21.7 months in the placebo arm.

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

The phase 3 ALSYMPCA trial[15] studied radium-223 in symptomatic men with progressive mCRPC with or without prior docetaxel exposure and no evidence of visceral metastasis. The trial reported improvement in median overall survival; 14.9 months versus 11.3 months (HR=0.70; 95% CI 0.58−0.83; p <0.001) in favor of radium-223 over placebo. Time to first skeletal-related event (SRE) improved from 9.8 month with placebo to 15.6 months with radium-223 (HR=0.66; 95% CI 0.52−0.83; p <0.001).

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

Optimal sequencing of agents in mCRPC remains an understudied area of research. As most of the agents approved for mCRPC were studied contemporaneously, the control arms typically were inactive agents such as prednisone or mitoxantrone.

The largest trial evaluating the sequencing of two androgen receptor-targeted therapies (ART) was performed in Canada and was a randomized phase 2 trial evaluating the sequence of abiraterone acetate plus prednisone followed by enzalutamide (group A) versus the opposite sequence (group B).[31] In this trial, 202 patients were randomly assigned to either group A (n=101) or group B (n=101). Time to second PSA progression was longer in group A than in group B (median 19.3 months versus 15.2 months; HR=0.66; 95% CI 0.45−0.97; p=0.036). PSA responses to second-line therapy were seen in 36% of patients for enzalutamide and 4% for abiraterone acetate. This study suggests that abiraterone acetate plus prednisone followed by enzalutamide would be the favored sequence in mCRPC if both agents were used.

31. In mCRPC patients who received prior docetaxel chemotherapy with or without prior abiraterone acetate plus prednisone or enzalutamide for the treatment of CRPC, clinicians may offer cabazitaxel. (Conditional Recommendation; Evidence Level: Grade B)

32. In mCRPC patients who received prior docetaxel chemotherapy and abiraterone acetate plus prednisone or enzalutamide, clinicians should recommend cabazitaxel rather than an alternative androgen pathway directed therapy. (Strong Recommendation; Evidence Level: Grade B)

Cabazitaxel was approved as second-line chemotherapy in 2010 based on the results of the TROPIC trial.[14] TROPIC randomized 755 men with mCRPC who had previously received docetaxel chemotherapy and demonstrated median survival of 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The HR for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0.70 (95% CI 0.59−0.83; p <0.0001).

Abiraterone acetate and enzalutamide were not available at the time of the TROPIC trial, so it is unknown if this would have influenced the positive outcomes seen in TROPIC.

Optimal third line therapy for mCRPC is unknown. The majority of patients will receive one ART with abiraterone acetate plus prednisone or enzalutamide and docetaxel chemotherapy. The CARD trial[32] tested the efficacy and safety of cabazitaxel versus the alternative ART therapy in patients with mCRPC who progressed after two prior therapies. A total of 255 patients were randomized, and progression or death was reported in 73.6% in the cabazitaxel group compared with 80.2% in the group that received a second ART (HR=0.54; 95% CI 0.40−0.73; p <0.001). The median OS was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling-targeted inhibitor (HR for death =0.64; 95% CI 0.46−0.89; p = 0.008).

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

In the randomized, open-label, phase 3 PROfound trial,[33] de Bono et al. randomly assigned 387 patients with progression on enzalutamide or abiraterone acetate (2:1) to receive olaparib or the physician's choice of enzalutamide or abiraterone acetate (control). All patients had a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A had at least one alteration in BRCA1, BRCA2, or ATM; cohort B had alterations in any of 12 other prespecified genes. Median OS in cohort A was 18.5 months with olaparib compared to 15.1 months in the control group. Investigators noted that anemia and nausea were the main toxic effects seen in patients on olaparib.

In addition to olaparib, rucaparib is also FDA approved for patients with deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Platinum-based chemotherapy also has a mechanism of action that correlates with defects in homologous recombination DNA repair. Preliminary data have demonstrated that, similar to PARP inhibition, carboplatin may improve outcomes in men

with similar DNA defects.[34] However, to date there are no randomized data supporting its use.

34. In patients with mismatch repair deficient or microsatellite instability high mCRPC, clinicians should offer pembrolizumab. (Moderate Recommendation; Evidence Level: Grade C)

In a case series of 1,033 patients with advanced prostate cancer, 3.1% had a microsatellite instability-high/mismatch repair deficient prostate cancer, with more than half of those treated with anti PD-1 therapy responding to treatment having a >50% decline in PSA.[35]

In May 2017, the FDA approved pembrolizumab for patients with any metastatic, microsatellite instability-high or mismatch repair deficient histology who have progressed following prior treatment and who have no satisfactory alternative treatment options.[36]

Bone Health. Several factors conspire to place the average patient with metastatic prostate cancer at a higher risk of bone complications. First, the median age of onset of the disease is in the late 60s, meaning that the average patient with metastatic disease may be in his 70s (or beyond), clearly a population at risk of physiologic, age-related decreases in bone mineral density. Secondly, a primary therapeutic intervention in patients with recurrent disease (ie, 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.[37,38] Finally, in patients with advanced disease, bones are the most common site of metastatic disease, with many patients at some point in their course demonstrating evidence of disease in this site.

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

36. Clinicians should recommend preventative treatment for fractures and SREs, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to advanced prostate cancer patients on ADT. (Clinical Principle)

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

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

FUTURE DIRECTIONS

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with advanced prostate cancer. While dramatic recent advances have been made, there are many unmet needs in prostate cancer management. As we move forward as a field, we need to focus on the biologic make-up of tumors and how these can be better leveraged to identify treatment options for patients.

Disclaimer: This document was written by the Advanced Prostate Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2018. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology, oncology, and radiation oncology with specific expertise on this disease space. The mission of the panel was to develop recommendations that are analysis based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of advanced prostate cancer. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available

prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

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