CASTRATION-RESISTANT PROSTATE CANCER

AUA Guideline (Amended 2018)

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. These patients represent a relatively common clinical presentation and the earliest clinical manifestation of castration resistance.

- *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)*
- *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)*
- *Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (i.e. abiraterone + 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)*

This pocket card was developed as a summary of the full AUA Guideline for this subject. The complete AUA Guideline (available at www.AUAnet.org/Guidelines) should be consulted as the final authority. Please review the online guideline for more information on the appropriate application of the document.

- *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

Asymptomatic or minimally symptomatic, mCRPC with no 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 attributable to his prostate cancer. However, one must then consider whether the patient required 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.

- *Clinicians should offer abiraterone + 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 + prednisone and enzalutamide] /B [docetaxel and sipuleucel-T])*
- *Clinicians may offer first- generation anti-androgen therapy, ketoconazole + 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

Symptomatic, mCRPC with good performance status and no prior 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.

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

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 III 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 quality of life.

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

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 castrate-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.

- *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 + prednisone and enzalutamide] / B [cabazitaxel])*
- *Clinicians may offer ketoconazole + steroid to patients with mCRPC with good performance status who received prior docetaxel chemotherapy if abiraterone + prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)*
- *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)*
- *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

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. They advocate

for an increasing emphasis on a patient's quality of life and concentrate 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.

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

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, androgen-deprivation therapy, 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. 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.

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

The complete Castration-Resistant Prostate Cancer Guideline is available at **www.AUAnet.org/Guidelines**.

APPENDIX A: ECOG PERFORMANCE STATUS

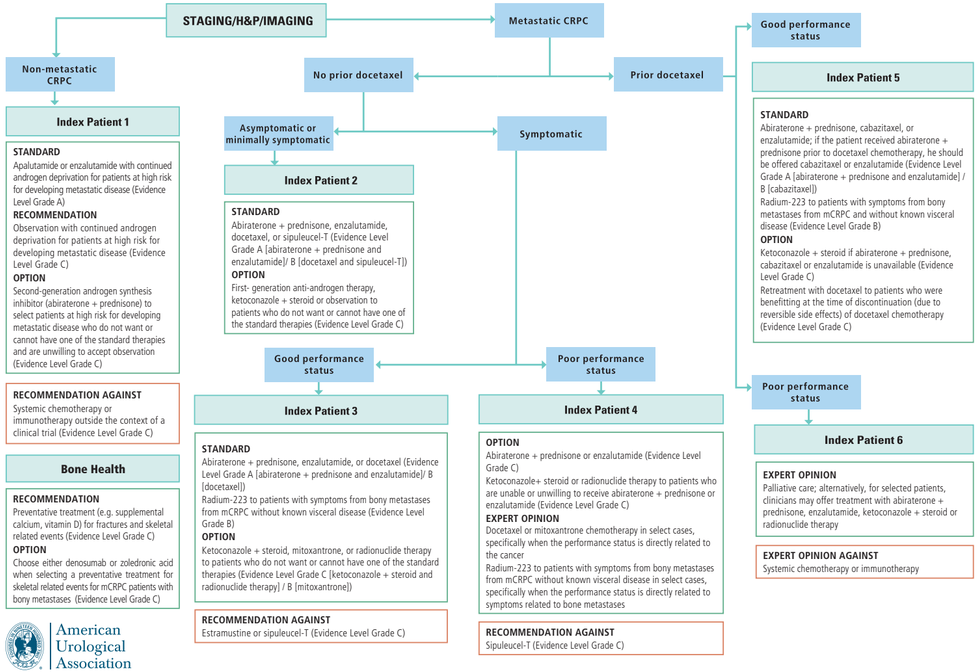
ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Castration-Resistant Prostate Cancer: AUA Guideline 2018



American Urological Association

Advancing Urology™

2018

CASTRATION-RESISTANT PROSTATE CANCER:

AUA GUIDELINE

(AMENDED 2018)

for Urologists

American Urological Association

Education & Research, Inc.

Advancing Urology™