

## AMENDMENT SUMMARY

### Castration-Resistant Prostate Cancer (CRPC) Guideline Amendment 2018

#### Amendment Panel

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**Purpose:** One of the first clinical presentations of CRPC occurs in a patient with a rising PSA despite medical or surgical castration. For the purposes of this Guideline, these patients are Index Patient 1. 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. Until recently, no agent had been shown to demonstrate significant benefits in large Phase 3 trials in the non-metastatic CRPC patient population.

#### Updated 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 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 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.

**Peer Review and Approval:** The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the treatment of CRPC. In addition to nominated reviewers and those submitting public comments, the document was also reviewed internally by the AUA Practice Guidelines Committee (PGC), Science and Quality Council (SQC), and Board of Directors (BOD). The draft guideline document was distributed to 54 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 20 reviewers provided comments. At the end of the peer review process, a total of 59 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC and BOD for final approval.

## Summary of Guideline Changes

**New 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 and was granted FDA approval 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.<sup>17</sup>

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.<sup>8</sup> All patients had a diagnosis of non-metastatic CRPC with a PSA doubling time  $\leq 10$  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  $\geq 15\%$  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.<sup>18</sup> This drug binds AR with a five- to eight-fold higher affinity than bicalutamide.<sup>18</sup>

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.<sup>19</sup> All patients had M0 CRPC with a PSA doubling time  $\leq 10$  months (median PSA doubling time, 3.7 months) and PSA  $\geq 2$  ng/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.<sup>20</sup> 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  $\geq 50\%$  and  $\geq 90\%$  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.

**New 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.

**New Statement 3:** 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)

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. This treatment is also associated with fewer serious adverse events compared to other available therapies, such as ketoconazole or first-generation anti-androgens. While abiraterone is considered a standard therapy in other patient populations, it is not FDA-approved for non-metastatic patients. 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.

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.<sup>21</sup> 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 mCRPC prior to chemotherapy; the indication was then expanded for patients pre-chemotherapy. Though it is generally well tolerated, 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.

### **Supporting Text**

Information regarding closed clinical trials was removed from the future directions section. All necessary references were updated as well.

The remaining statement for Index Patient 1 (now Guideline Statement 4) as well as all other statements related to Index Patients 2-6 are unchanged.

## Updated References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7.
19. Hussain M, Fizazi K, Saad F et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018; **378**: 2465.
20. Penson DF, Armstrong AJ, Concepcion R et al: Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. *J Clin Oncol* 2016; **34**: 2098.

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