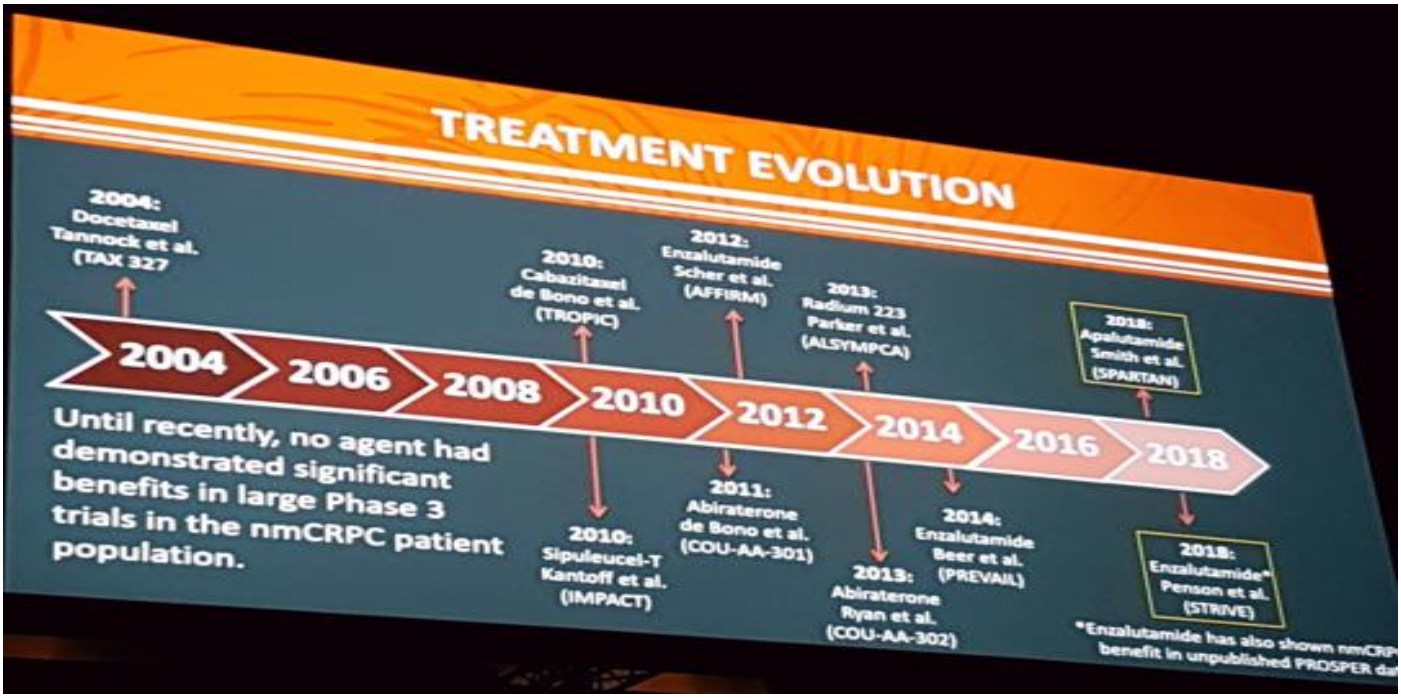
AUA 2018: Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2018

San Francisco, CA (UroToday.com) David F. Jarrard, MD provided an update on the CRPC AUA guideline amendment at 113th Annual Scientific Meeting of the American Urological Association (AUA). Dr. Jarrard highlights, the six index patients associated with the CRPC guidelines assists in clinical decision making, representing the most common clinical scenarios that are encountered in clinical practice. Guideline statements are developed to provide a rational basis for treatment based on currently available published data. The purpose of this guideline amendment is essentially to update current management of index patient 1: asymptomatic non-metastatic CRPC (nmCRPC). These patients are typically defined as having a rising PSA and no radiologic evidence of metastatic disease. Based on the PCWG2 PSA only failure, this includes a risking PSA greater than 2 ng/mL higher than the nadir, a rise at least 25% over nadir, and a rise confirmed by a 2nd PSA at least 3 weeks later.

The fields of GU Oncology and Urology are advancing rapidly including new treatments, enrolling clinical trials, screening and surveillance recommendations along with updated guidelines. Join us as one of our subscribers who rely on UroToday as their must-read source for the latest news and data on drugs. Sign up today for blogs, video conversations, conference highlights and abstracts from peer-review publications by disease and condition delivered to your inbox and read on the go.

Metastatic CRPC is a uniformly fatal disease, with a median survival of ~2.5 years. mCRPC can develop from (i) metastatic hormone-sensitive prostate cancer (HSPC) that has developed resistance to ADT, and (ii) nmCRPC that has developed resistance to ADT. The metastases associated with mCRPC are a major cause of morbidity and mortality. Men with nmCRPC with a PSA doubling time of <8-10 months are at significant risk for metastatic disease and prostate cancer-specific death. Prevention of metastases represents a major unmet need to these patients. As Dr. Jarrard highlights, the treatment evolution for CRPC since 2004 is impressive:



To add the amendment to the CRPC guidelines (which is amendment #3), the committee undertook a systematic review from February 2015 to May 2018, identifying five articles relevant to nmCRPC.

Index Patient 1 – Guideline Statement 1:
Clinicians should offer apalutamide or enzalutamide with continued androgen deprivation to patients with nmCRPC at high risk for developing metastatic disease (Standard; Evidence Level Grade A [apalutamide]/Grade B [enzalutamide])

In 2018, apalutamide became the first FDA-approved treatment for patients with nmCRPC. Apalutamide is a nonsteroidal anti-androgen AR inhibitor, which binds to the ligand-binding domain of the AR. AR inhibition is secondary to nuclear translocation and DNA binding, with 7-10-fold higher affinity than bicalutamide. Presented at GU ASCO and published in the *New England Journal of Medicine*[1] was the SPARTAN trial which randomized 1207 men 2:1 to receive apalutamide vs placebo. In the planned primary analysis at 378 events, median metastasis-free survival was 40.5 months in the apalutamide group compared with 16.2 months in the placebo group (HR for metastasis or death 0.28, 95% CI 0.23-0.35). Time to symptomatic progression was significantly longer with apalutamide than with placebo (HR 0.45, 95%CI 0.32-0.63). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group. The conclusions from SPARTAN were that apalutamide decreased the risk of metastasis or death by 72% and prolonged the median MFS by more than two years in men with high-risk nmCRPC. Furthermore, the MFS benefit was consistent across all subgroups, and the results were supported by consistent improvement across all evaluable endpoints (time to metastasis, PFS, time to symptomatic progression, time to PSA progression, and PSA decline).

Enzalutamide is a novel AR signaling competitive inhibitor of androgen binding. It inhibits nuclear translocation of the AR, DNA binding, and coactivator recruitment. Enzalutamide binds the AR with a 5-8-fold greater affinity than bicalutamide. The STRIVE trial was a mixed population of men diagnosed with non-metastatic (n=139) or metastatic (n=257) CRPC randomized 1:1 to receive enzalutamide (160 mg/day) or bicalutamide (50 mg/day), with both arms remaining on ADT[2]. Enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (HR 0.24, 95%CI 0.18-0.32). Enzalutamide resulted in significant improvements in all key secondary end points: time to PSA progression (HR 0.19, 95%CI 0.14-0.26), proportion of patients with a ≥ 50% PSA response (81% v 31%; P < .001), and radiographic PFS in metastatic patients (HR 0.32, 95%CI 0.21-0.50). Beneficial effects with enzalutamide were observed in both nonmetastatic and metastatic subgroups. The PROSPER trial is currently only available in abstract form[3] and therefore was not used in the assessment of enzalutamide for this patient population. However, abstract data does support its use in the nmCRPC population. In this trial, 1,401 patients were randomized 2:1 enzalutamide vs placebo, with a primary outcome of MFS. Secondary endpoints were time to PSA progression, time to first use of new therapy, and OS. Enzalutamide was associated with a 71% improvement of MFS (HR 0.29), as well as time to PSA progression (HR 0.07), and time to subsequent therapy (HR 0.21). At the interim analysis for OS, the HR was 0.80 (favoring enzalutamide), but was not statistically significant (p=0.15).

Index Patient 1 – Guideline Statement 2:
Clinicians may recommend observation with continued androgen deprivation to patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies (Recommendation; Evidence Level Grade C)

Index Patient 1 – Guideline Statement 3:
Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (i.e. abiraterone + prednisone) to select patients with nmCRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies and are willing to accept observation (Option; Evidence Level Grade C)

Index Patient 1 – Guideline Statement 4:
Clinicians should not offer systemic chemotherapy or immunotherapy to patients with nmCRPC outside the context of a clinical trial (Recommendation; Evidence Level Grade C)

Presented by: David F. Jarrard, MD, University of Wisconsin School of Medicine, Madison, WI

WATCH: AUA Castration-Resistant Prostate Cancer Guidelines - Interview with Michael Cookson

References:

1. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378(15):1408-1418.
2. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE Trial. *J Clin Oncol* 2016;34(18):2098-2106.
3. Hussain M, Fizazi K, Saad F, et al. PROSPER: A phase 3, randomized, double-blind, placebo-controlled study of enzalutamide in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). *J Clin Oncol* 2018;36(suppl 6S;abstr 3).

Written by: Zachary Klaassen, MD, Urologic Oncology Fellow, University of Toronto, Princess Margaret Cancer Centre at the 2018 AUA Annual Meeting - May 18 - 21, 2018 – San Francisco, CA USA