



Debu Tripathy, MD
Editor-in-Chief

Staying Ahead of the Curve of Anti-Androgen Therapy Resistance

Blockade of the androgen receptor (AR) pathway remains the mainstay of systemic therapy for prostate cancer. Not only have newer anti-androgen agents been approved in recent years for clear benefits in the advanced setting, but there are also increasing roles for androgen deprivation earlier in the course of the disease. From the time that Huggins initially demonstrated that androgens are the drivers of prostate cancer and showed a clinical benefit of castration¹, to the subsequent discovery of mutations in genes involved in the AR pathways and in AR itself², the central role of this pathway continues to drive new treatment paradigms. By the same token, clinical resistance to AR inhibitors has been an active area of research—in fact, the definition of true “castration-resistant” prostate cancer (CPRC) is becoming a moving target as newer drugs are addressing strategies that attack different elements of the AR machinery in CPRC.

In this issue of *The American Journal of Hematology/Oncology*[®], Dr Dreicer navigates us through some of the clinical dilemmas that arise in the sequencing of hormonal therapy, and using principles of cross-resistance among these agents to optimize strategies over time. Importantly, clinical observations of efficacy of abiraterone before or after the anti-androgen receptor inhibitor enzalutamide given in sequence have ramifications that are detailed in the context of specific clinical scenarios. Additionally, insights gained from biological studies of CPRC have informed future strategies—for example, the fact that resistance results from the abilities of prostate cancer cells to synthesize its own androgens for precursors has provided the basis for the development of drugs such as abiraterone, which inhibits the cytochrome P450 enzyme, CYP17, which participates in the activity of both 17 α -hydroxylase and 17,20-lyase, and thus provides activity in “CPRC.” However, more specific inhibitors of this biosynthetic pathway, particularly those that act more distally and immediately prior to generation of the more potent androgens will be important areas of progress that may extend the benefits that might still be derived in seemingly hormonally resistant disease. Dr Dreicer’s review also delves into consequences of activating mutations in one of these enzymes (3 β HSD1) and strategies to overcome this anomaly that would naturally lead to hormonal resistance. Read on to integrate biological nuances in addressing decisions in the clinic and framing future drug and biomarker development strategies emerging for refractory prostate cancer.

REFERENCES:

1. Huggins C, Stevens Jr. RE, Hodges CV. The effect of castration on advanced carcinoma of the prostate gland. *Arch Surg.* 1941;43:209-223. doi:10.1001/archsurg.1941.01210140043004
2. Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med.* 1995;332:1393-1398.

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