Steroid Sidestep: Evading Androgen Ablation by Abiraterone
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Tumor mechanisms of abiraterone resistance in clinical prostate cancer are not well defined. Chen and colleagues report that a T878A androgen receptor mutation occurs in a subset of patients progressing while receiving abiraterone, suggesting that this may be a therapeutically exploitable mechanism of abiraterone resistance in castration-resistant prostate cancer. Clin Cancer Res; 21(6); 1240–2. ©2014 AACR.

See related article by Chen et al., p. 1273
The lower frequency of the AR T878A mutation in patients treated with the combination of abiraterone, dutasteride, and prednisone (1 of 14), as compared with abiraterone alone, might indicate that dutasteride and/or prednisone inhibits enrichment of mutation-bearing tumor cells. Although suggestive, the number of patients in each group is small and not enough for a definitive comparison. Notably, glucocorticoids (including prednisone), which are usually administered with abiraterone to suppress mineralocorticoid excess, may also suppress abiraterone-mediated progesterone upregulation (11). Furthermore, as the authors point out, it is possible that selection for the AR T878A mutation is not directly due to progesterone and is instead driven by another 21-carbon steroid that serves as an AR agonist in this context.

The most important clinical implication of these findings from Chen and colleagues is that this study seems to have identified a therapeutically exploitable mechanism of abiraterone resistance. Enzalutamide is effective in blocking the AR T878A-mutant AR and abiraterone-resistant tumor progression. Figure 1. Simplified schema of progesterone stimulation of the AR T878A mutation in abiraterone-resistant prostate cancer. A, CYP17A1 is required for androgen synthesis and wild-type AR-dependent tumor progression and leads to an increase in progesterone synthesis. B, abiraterone blocks androgen synthesis and wild-type AR-dependent tumor progression. C, progesterone stimulates the T878A-mutant AR and abiraterone-resistant tumor progression.

**Disclosure of Potential Conflicts of Interest**

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