Re: Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms that Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven
Attard G, Reid AH, Yap TA, et al.
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Expert’s summary:
Abiraterone acetate, a small molecule inhibitor of cytochrome P17 (CYP17), inhibits 17 alpha-hydroxylase and C17, 20 lyase, both key enzymes in androgen synthesis. It was tested in 21 chemotherapy-naive men with metastatic prostate cancer that was resistant to multiple hormone therapies. Once-daily oral abiraterone acetate was given at doses of 250 mg, 500 mg, 750 mg, 1000 mg, and 2000 mg and resulted in dramatic declines in serum testosterone, estradiol, dehydroepiandrosterone (DHEA), and androstenedione. Such declines were paralleled by rapid declines in prostate-specific antigen (PSA) of >30%, 50%, and 90% in 14 (66%), 12 (57%), and 6 (29%) patients, respectively. Radiographic regression of disease, normalization of lactate dehydrogenase (LDH), and reduced pain from prostate cancer with reduced analgesic use were also documented. Even when PSA and radiographic progression occurred on drug, hormone levels did not rise. Abiraterone was well tolerated, although secondary mineralocorticoid excess upstream of the CYP17 blockade commonly induced hypertension, hypokalemia, and edema. Dexamethasone 0.5 mg/d suppressed the mineralocorticoid excess symptoms. The 1000 mg/d dose cohort was expanded at the Royal Marsden Hospital and showed dramatic endocrine, antitumor activity, confirming the hypothesis that castration-resistant prostate cancer remains dependent on androgen receptor signaling.

Expert’s comments:
This study is the first-long term study in man to establish the safe and effective use of CYP17 inhibition. Subsequent phase 2 studies of this agent have been conducted at the University of California San Francisco, the MD Anderson Cancer Center in Dallas, Texas, and the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. At the American Society of Clinical Oncology’s 2008 annual meeting, all of these papers were reported and confirmed the substantial effect of this agent in castration-resistant prostate cancer [4]. The MSKCC study in particular showed that 40–50% of patients with castration-resistant and docetaxel-resistant prostate cancer had PSA and radiographic regression. Collectively, these observations led to a large international phase 3 trial in which patients with docetaxel-resistant prostate cancer are randomized in a 2:1 ratio to either abiraterone or placebo. This trial has accrued >900 patients, is accruing >100 patients per month, and should reach its accrual goal of 1300 patients soon. A second study is planned in patients who are docetaxel naïve. Hopefully, these data will lead to regulatory-agency approval of this novel agent in the near term. Whether this drug can replace luteinizing hormone-releasing hormone agonists is, of course, an open question.

Other companies have begun to develop new agents that also target the CYP17 enzymes, and it is expected that competitors to this abiraterone molecule soon will appear.

Conflicts of interest: Dr. Vogelzang has served on the Cougar Medical advisory board, and the Nevada Cancer Institute participates in the abiraterone phase 3 clinical trial.

References

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