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FDA Approves New Weapon in Widening War on Prostate Cancer

By Tyler Smith

After a two-decade dry spell, a relative flood of new drugs to treat prostate cancer has hit the market in the past 30 months. The latest to receive U.S. Food and Drug Administration approval is a once-a-day tablet shown to improve survival rates by nearly five months for men with prostate cancer who have previously received chemotherapy treatment.

The drug, enzalutamide (trade name Xtandi), won FDA approval Aug. 31, and should be available to patients this month. The date is to be announced on the Web site of the manufacturer, San Francisco-based Medivation.

It's the sixth agent approved for treatment of castrate-resistant prostate cancer (CRPC) since April 2010, when the immunotherapy Provenge became available (*Insider*, May 12, 2010). It's another option for clinicians waging a fight against the second-leading cancer among men.

The phase III multicenter clinical trial of enzalutamide involved 1,200 patients with CRPC who had been treated with the chemotherapy agent docetaxel (trade name Taxotere). The patients were randomized, with two receiving enzalutamide for every one who received a placebo.

Patients treated with enzalutamide had a median survival rate of 18.4 months, compared with 13.6 months for the placebo group.

Success in tough cases. The results are especially significant given the very ill group of patients involved in the trial, said E. David Crawford, MD, head of the Urologic Oncology program at University of Colorado Hospital. Several patients receiving treatment at UCH enrolled in the trial, Crawford said.

> *"These were patients with advanced prostate cancer who had failed chemotherapy and were at the end of the line," Crawford said.*

The new drug is a third-generation class of medications that prevent male hormones, or androgens, especially testosterone, from tightly binding to androgen receptors in the cell. In cancer patients, that binding allows testosterone to move into the nuclei of the cells, where it causes the abnormal division that is the hallmark of cancer.

Urologic Oncology chief Crawford says FDA approval of Xtandi gives clinicians a potent new treatment for prostate cancer and more opportunities to explore combination therapies and earlier treatment.

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Testosterone can be produced by the testes, the adrenal gland and even the cancer itself, Crawford explained. Xtandi disrupts testosterone's cancer-causing mission by binding itself tightly to the androgen receptor. "That keeps the testosterone away," he said. "If you take away the testosterone, the [cancer] cells die."

Taking on testosterone. Researchers have long targeted testosterone in the fight against prostate cancer. Michael Glodé, MD, of the University of Colorado Cancer Center, worked on the FDA trial that resulted in approval for the testosterone-suppressing drug leuprolide (trade name Lupron), which is injected in men with advanced prostate cancer.

This study was being completed when Crawford arrived at UCH in 1986. Building on the work of Glodé, Crawford did a trial which added the oral anti-androgen flutamide (Eulexin) to the Lupron.

Crawford co-authored a 1989 *New England Journal of Medicine* (NEJM) paper showing that men who received combination therapy of the leuprolide injection and flutamide lived an average of 7.3 months longer than those who received the injections alone.

More recently, the hospital was involved in the trial of abiraterone acetate (trade name Zytiga), a daily tablet that is combined with prednisone to eliminate testosterone production. Thomas Flaig, MD, medical oncologist at UCH's Tony Grampsas Urologic Oncology Clinic and assistant professor at the School of Medicine, co-authored a May 2011 *NEJM* article that reported the results of the clinical trial that led to FDA approval for abiraterone (*Insider*, June 9, 2011).

With each of these treatments, Crawford said, "the concept was the same: total androgen ablation. Our goal is to neutralize the source of the androgen as effectively as possible."

But Xtandi, he said, is "ten times more potent" than the combination injection/oral therapy he trialed in 1989. And patients take a once-daily regimen of four 40-milligram pills, an easier course than the two-tablet, thrice-daily routine flutamide alone requires.

Encouraged by the recent spate of drug approvals after a 20-year drought, Crawford believes the new treatments might be combined with other approaches, like chemotherapy and injections, and administered to patients earlier. He and Flaig co-authored an article discussing potential combinations of the new agents and how they might be sequenced in treatment in the January 2012 issue of *Oncology*.

"The idea is to move up these treatments for the newly diagnosed," Crawford said. "And in caring for prostate and other cancers, it's natural to look for ways to combine these therapies, not as a cure, but to make cancer a chronic disease."