

With enzalutamide for prostate cancer, it may all depend on the tumor's AR profile

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Enthusiasm continues in the medical community anxious for effective agents for men with metastatic castration-resistant prostate cancer (mCRPC). Most prostate cancer patients who develop metastatic disease are initially treated with readily available luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, with or without an anti-androgen. The rationale here is to decrease androgen levels and/or block androgen receptor (AR) binding. In patients whose disease becomes refractory to this front-line hormonal deprivation, the molecular mechanisms involved in androgen independence include androgen receptor gene amplification, AR mutations that allow stimulation by a variety of weak androgens, and AR activation by autocrine production of androgens from tumor cells. Patients with metastatic castration-resistant prostate cancer (mCRPC) who biochemically recur after androgen-deprivation therapy with significant prostate-specific antigen (PSA) elevations and/or who develop radiographic or symptomatic metastases are then usually considered for cytotoxic chemotherapy.

The only approved initial cytotoxic chemotherapeutic agent that has demonstrated improved survival for patients with mCRPC is docetaxel. For patients who fail docetaxel, cabazitaxel with prednisone is an approved second-line treatment. Similarly, another approved second-line treatment (albeit, hormonal) for patients who have failed docetaxel therapy is abiraterone acetate, which attacks the adrenal and extragonadal synthesis of androgen. The magnitude of this effect was not appreciated until it was recognized that the androgen receptor and ligand-dependent androgen receptor signaling remain active and upregulated in men with castrate levels of testosterone (≤ 50 ng/dL).¹ Recognition of the importance of the signaling of the androgen receptor and its seemingly independent behavior in a milieu of little or no androgen is now appreciated. Chen et al. reported in 2004 on the

development of a second-generation potent oral non-steroidal antiandrogen (MDV3110, ie, enzalutamide).² This agent blocks AR binding with testosterone, blocks nuclear translocation of the AR from the cytoplasm, and blocks DNA binding and activation.³ It is novel in that unlike the established antiandrogens (bicalutamide, flutamide, nilutamide), it binds potently to the AR, does not stimulate the AR in mCRPC, has no measurable agonistic activity, and induces death in prostate cancer cells that were previously resistant to hormone-based therapies.

Scher et al have reported on 1,199 patients in the AFFIRM trial in which the primary endpoint was to evaluate survival in patients who had been previously treated with docetaxel and were randomized to receive placebo or enzalutamide.⁴ In addition to showing significant increases in survival – 18.4 months in the enzalutamide group, compared with 13.6 months in the placebo group – the study also demonstrated improved secondary endpoints (PSA response rates, soft-tissue response rates, time to progression, radiographic progression-free survival). In addition, the incidence of high-grade side effects was higher in the placebo group, which suggested that enzalutamide was relatively more effective in ameliorating disease-related symptoms than was placebo. However, the agent does cross the blood-brain barrier and 5 patients (0.6%) in the enzalutamide group experienced seizures, which generated concern for use of the drug in patients with nonmetastatic central nervous system issues.

Another exciting trial of enzalutamide, which was fully enrolled in 2012 in advance of its anticipated end enroll date (2013), is the PREVAIL trial.⁵ This is a phase 3 multinational, double-blind, placebo-controlled study of patients at 222 study sites. The purpose of this randomized trial is to learn of potential benefit in overall survival and progression-free survival in chemotherapy-naïve men with progressive metastatic prostate cancer who have failed front-line androgen-

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deprivation therapy and who were randomized to receive either enzalutamide or placebo. The results of this trial and subsequent analysis should be available later this year or in early 2014. In addition, with our knowledge now of the importance of the AR receptor and any available androgen, there is impetus for a trial of a novel AR target signaling inhibitor such as enzalutamide with an androgen synthesis inhibitor such as abiraterone.

As promising as this novel AR inhibitor enzalutamide seems to be, we may have to temper some of our enthusiasm as it is unlikely that all men with mCRPC will benefit. About 25% of the tumors that were analyzed from men with mCRPC had no androgen receptors and demonstrated marked upregulation of mitotic genes independent of AR regulation.⁶ Nonetheless, it appears that we are making progress in extending over-

all and progression-free survival through multiple approaches on an array of targets.

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