Beyond Approval: What Is the Most Appropriate Way to Use the Expanding Armamentarium in Metastatic Castration-resistant Prostate Cancer and How Do We Move Forward?

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In this issue of *European Urology*, Dana Rathkopf and colleagues update the data previously reported on the Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients with Metastatic Castration-resistant Prostate Cancer trial (COU-AA-302), after a third interim analysis, conducted after 56% of expected deaths [1]. The findings from the prior analysis were largely upheld in this update (no real news here!). The hazard ratio (HR) for radiographic progression-free survival was 0.52 (0.53 previously); the HR for overall survival was 0.79 (0.75 previously) with additional clarity on the tail. However, as with the prior analysis, the HR for overall survival did not meet the prespecified boundary for significance. Importantly, the safety signal remained favorable for abiraterone, with a modestly increased number of grade 3 or 4 adverse events over placebo (49% vs 44%), similar to the 6% increase seen in the prior analysis. Measures of mineralocorticoid toxicity also remained similar over time, with a 3% increase in cardiac disorders occurring with abiraterone over placebo.

In addition to the COU-AA-302 trial, the Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-naive Patients with Progressive Metastatic Prostate Cancer (PREVAIL) phase 3 trial of enzalutamide versus placebo in chemotherapy-naive patients was also recently reported [2]. In this trial, after a median follow-up of 20 mo, enzalutamide demonstrated improvements in overall survival (HR: 0.71) and radiographic progression-free survival (HR: 0.19).

The initial trials with abiraterone (COU-AA-301) and enzalutamide (the Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-resistant Prostate Cancer Previously Treated with Docetaxel-based Chemotherapy trial [AFFIRM]) that resulted in the US Food and Drug Administration (FDA) approval of these two compounds for metastatic castration-resistant prostate cancer (mCRPC) were conducted in patients who demonstrated evidence of disease progression after docetaxel-based chemotherapy. Based on COU-AA-302, abiraterone has received FDA approval for chemotherapy-naive patients, and it is likely that the same will happen with enzalutamide based on the PREVAIL data. The assumption that chemotherapy will be offered primarily to patients with evidence of disease progression after androgen-receptor (AR)-targeted compounds appears to be quite logical based on the four pivotal trials conducted with the two compounds.

However, the recently released results of the Eastern Cooperative Oncology Group 3805 trial (a randomized study of androgen-deprivation treatment [ADT] with or without docetaxel [the CHAARTED trial]) highlight the fact that the optimal sequence of systemic treatments in men with metastatic prostate cancer needs to be more carefully evaluated. In the CHAARTED trial, men with hormone-naive metastatic disease were treated either with ADT or ADT plus six cycles of standard dose docetaxel [3]. Patients with high-volume disease, manifested by at least four bone lesions or any extranodal visceral metastases, demonstrated 3-yr overall survival of 63.4% in the docetaxel and ADT group versus 43.9% for ADT alone. Although full publication of the results from this trial will be more informative, the preliminary data released indicate that the practice of
reserving taxane-based chemotherapy for patients with metastatic prostate cancer only as the last resort may have to be reevaluated.

With the relatively recent approval of various new agents for the treatment of mCRPC in clinical practice, more information on appropriate sequencing of active agents has become of primary importance. It is critical to recognize that pivotal trials are designed to test specific hypotheses that satisfy regulatory requirements for drug approval that may not adequately define the best use of a newly approved compound in clinical practice. In mCRPC, five new compounds (abiraterone, enzalutamide, radium-223, cabazitaxel, and sipuleucel-T) satisfied FDA criteria for approval in a relatively short period of time. All studies were designed using a placebo (with or without prednisone, as in the case of abiraterone, enzalutamide, and sipuleucel-T) or mitoxantrone and prednisone (in the case of cabazitaxel) or best symptomatic care plus a variety of treatments (in the case of radium-223).

The establishment of pre- and postdocetaxel spaces, which may make some intuitive sense, was also arbitrarily created to satisfy regulatory requirements and is thus an artificial construct. The COU-AA-301/302 and PREVAIL/AFFIRM studies were designed identically for each drug; the difference is that they were conducted separately in the “pre- and postchemotherapy spaces.” Why is this strategy necessary? Would COU-AA-301 alone not have been sufficient to determine the activity of abiraterone and justify approval for all mCRPC patients? By virtue of their design, these pivotal studies will not shed light on the best way to use these compounds in clinical practice. Should abiraterone be used first or vice versa? Are these compounds as active as the pivotal trials indicated if they are used sequentially in real life? Evolving data suggest that answering these questions will require additional large, randomized studies.

Sequential use of treatments with distinct mechanisms of action targeting the same oncogenic process (as is the case for AR targeting through suppression of androgen synthesis with abiraterone and for AR antagonism with enzalutamide) has resulted in interesting preliminary observations. Small retrospective studies describing the results with enzalutamide following abiraterone and vice versa [4,5] have indicated modest benefits (at best) with either compound used in the second-line setting demonstrated by infrequent reductions in prostate-specific antigen level (which is a hallmark for AR-targeting drugs) and a relatively short period of progression-free survival compared with the reports of randomized studies. If prospectively confirmed, the relative time on each drug based on the sequence will have implications for cost as well as the potential for differential efficacy.

Similar observations regarding a sequential use of AR-targeted compounds and docetaxel have been reported. Preliminary (retrospective) data in patients receiving docetaxel following abiraterone suggest a lower response to chemotherapy compared with patients who did not receive abiraterone [6]. Interestingly, preclinical data suggest that a potential mechanism of docetaxel activity in prostate cancer—nuclear transport of the AR—may be susceptible to cross-resistance [7].

Clearly, novel AR-targeting drugs (including those active against tumors expressing constitutively active splice AR variants, compounds that target the N-terminal domain of the AR, those that block AR binding to DNA, and so forth) and other active non–AR-targeted agents are needed. Immunotherapy is one such attractive area of investigation. Data from the Randomized, Double-blind, Phase 3 Trial Comparing Ipilimumab versus Placebo Following Radiotherapy in Subjects with Castration-resistant Prostate Cancer That Have Received Prior Treatment with Docetaxel (CA-043), which compared radiation therapy combined with either ipilimumab or placebo, suggest that targeting cytotoxic T-lymphocyte antigen 4 with ipilimumab may have some benefit for a selected group of patients with mCRPC [8].

An ongoing phase 3 trial (a Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC-V/F ± GM-CSF in Men with Asymptomatic or Minimally Symptomatic Metastatic Castrate-resistant Prostate Cancer [PROSPECT]) of PROSTVAC-VF may further define the potential for vaccine-based therapies in mCRPC and offer the opportunity for more active immune-based therapies for this disease [9].

Increasingly active therapies in mCRPC have led to men with advanced prostate cancer living longer. It is likely that the increased knowledge of the biologic processes associated with the progression of prostate cancer will help us to select and individualize treatment for our patients in clinical practice. Progress is needed to determine the optimal use of new agents and strategies to combat resistance. It is clear that the treatment landscape has changed dramatically from only a few years ago—a welcome development.

Conflicts of interest: Daniel Suzman has nothing to disclose. Mario Eisenberger has received honoraria from Bayer, Medivation, and Astellas; has served on advisory boards and as a consultant for Jansen, Ipsen, and Active Biotech; and has received support for clinical trials from a company he previously co-owned (Oncology Trials Insights). He has served on a data safety monitoring committee for Bristol Myers and Bayer, and has received research grants from Genentech, TOKAI, Agensys, and Sanofi.

References


