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Phase III data for abiraterone in an evolving landscape for castration-resistant prostate cancer

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Abstract

At the 2010 meeting of the European Society for Medical Oncology (ESMO), a landmark development in prostate cancer therapy was unveiled. In a phase III study, the CYP17 inhibitor abiraterone yielded a survival advantage over placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) who had progressed despite prior docetaxel therapy. The data for abiraterone follow the publication of successful phase III studies earlier this year supporting two mechanistically distinct agents--namely, the novel taxane cabazitaxel and the autologous dendritic cell vaccine sipuleucel-T. A challenge that lies ahead for the scientific community is to discern the appropriate positioning of abiraterone in an increasingly crowded therapeutic landscape. Several ongoing trials are examining the agent in earlier settings (i.e., a phase III in mCRPC pre-docetaxel, and smaller studies in combination with radiation therapy or as neoadjuvant pre-surgery for localized disease). Herein, several potential strategies for abiraterone are presented to clarify the clinical utilization of this agent in the future.

COMMENTARY

Until recently, the paradigm for metastatic castration-resistant prostate cancer (mCRPC) remained relatively straightforward. Docetaxel with prednisone remained the mainstay of treatment on the basis of two large, randomized studies which demonstrated an overall survival (OS) improvement—TAX 327 and Southwest Oncology Group (SWOG) trial 9916.[1,2] In the pre- and post-docetaxel space, level 1 evidence for other therapies was limited to studies emphasizing endpoints other than survival. Within the past year, this clinical landscape has been drastically altered by several landmark studies. First, therapy

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PARTICIPATION/CONFLICTS OF INTEREST

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with the autologous vaccine sipuleucel-T yielded an improvement in OS compared to placebo in the IMPACT study, which assessed a cohort of mCRPC patients who were largely docetaxel-naïve (85.6%).3 Thereafter, the TROPIC study demonstrated an improvement in OS with the novel taxane cabazitaxel compared to mitoxantrone in mCRPC patients with docetaxel-refractory disease.4

COU-AA-301 represents the most recent positive phase III trial in CRPC, assessing the novel CYP17 inhibitor abiraterone.5 CYP17plays a key role in testosterone biosynthesis, functioning in the conversion of pregnenolone to 17-α-hydroxypregnenolone (via a 17-α-hydroxylase), and in the subsequent conversion of this moiety to dehydroepiandrosterone (DHEA) via a 17,20 lyase.6 In its early development, abiraterone was noted to block testosterone biosynthesis in *in vivo* models at nanomolar concentrations.7 In a heterogeneous array of phase II studies, abiraterone demonstrated provocative clinical efficacy in both chemotherapy-naïve and docetaxel-treated patients.[8–12] The encouraging data from these early experiences culminated in the design of phase III studies. COU-AA-301 was initiated in April of 2008, and randomized a total of 1,195 patients with docetaxel-refractory CRPC to either abiraterone or placebo in a 2:1 fashion (both arms received concomitant prednisone therapy). Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0–1 *v* 2), number of lines of prior chemotherapy (1 *v* 2), pain score (assessed by the Brief Pain Inventory, BPI), and the nature of progression (defined by prostate-specific antigen (PSA), radiograph, or both). The primary endpoint of the study was OS, with 85% power to detect a 25% improvement. Secondary efficacy endpoints included time to PSA progression (TTPP), PSA response rate (PSA RR), and radiographic progression-free survival (rPFS).

The median age of the study participants was 69 years, and the majority were Caucasian (93.1%).[5] A small proportion of patients enrolled were classified as ECOG performance status 2 (10.8%) or had received 2 lines of prior chemotherapy (28.3%). On August 20, 2010, following the first planned interim analysis, an independent data monitoring committee recommended that the study be un-blinded. At this point, abiraterone-treated patients had received a median of 8 cycles of therapy, compared to a median of 4 cycles of placebo in the control arm. Treatment with abiraterone resulted in an improvement in OS from 10.4 to 14.8 months (HR 0.646, 95%CI 0.54–0.77; $P < 0.0001$), and this benefit appeared across multiple subgroups. Abiraterone therapy also yielded superior outcomes with respect to TTPP (10.2 *v* 6.6 months, $P < 0.0001$), rPFS (5.6 *v* 3.6 months, $P < 0.0001$), and PSA RR (confirmed: 29.1% *v* 5.5%, $P < 0.0001$). The overall frequency of adverse events amongst placebo-treated patients exceeded that amongst abiraterone-treated patients. However, several grade 3/4 toxicities did occur more frequently with abiraterone therapy, including fluid retention (2.3% *v* 1.0%), hypokalemia (3.8% *v* 0.8%), hypertension (1.3% *v* 0.3%), and cardiac disorders (4.1% *v* 2.3%).

Where should abiraterone fall into currently existing algorithms? The clinician should be forewarned that an ongoing phase III clinical trial may lead to implementation of the agent in earlier settings. For instance, a phase III study randomizing mCRPC chemotherapy-naïve patients to abiraterone or placebo is ongoing, with an estimated primary completion date in April of 2011.[13] Other efforts seek to position abiraterone even earlier in the therapeutic continuum. One representative phase II trial combines abiraterone with endocrine therapy and external beam radiation in intermediate- and high-risk localized disease.[14] Additionally, a randomized, phase II study compares traditional endocrine therapy with or without abiraterone as preoperative treatment for high-risk, localized prostate cancer.[15] With the evolution of these trials, it is unlikely that the clinical positioning of abiraterone will remain stagnant. However, it should be noted that only the phase III data will likely result in regulatory changes.

In short course, the oncologist will be faced with a unique clinical dilemma--specifically, multiple therapeutic options for the patient with CRPC. Cabazitaxel has been approved by the US Food and Drug Administration (FDA) in this setting, and abiraterone will likely follow suit. Furthermore, data from several large, randomized trials of other potential agents in the docetaxel-refractory space may soon be available. As two prominent examples, encouraging results were seen in early clinical testing for the novel antiandrogen MDV3100 and the selective 17,20-lyase inhibitor TAK-700.[16,17] Both are currently being compared to placebo in phase III studies enrolling patients with docetaxel-refractory mCRPC.[18,19] How will the oncologist discern amongst these choices?

Looking ahead, the research community may utilize one of several strategies to resolve a state of equipoise for the docetaxel-refractory mCRPC patient. Comparative trial designs represent an obvious approach, although such studies will require vast resources to explore already existent therapies. Combinatorial designs may open new therapeutic avenues--for example, MDV3100 in combination with TAK-700 or abiraterone has theoretical rationale, allowing for dual targeting of endocrine signaling axes. Alongside these clinical efforts, the development of predictive biomarkers is crucial, as this may offer an individually-tailored approach to therapy. In a cohort of 598 prostate cancer patients (with a heterogeneous array of clinicopathologic features), a specific CYP17 lyase single nucleotide polymorphism (SNP; variant A allele in rs10883783) was associated with a 56% reduction in prostate cancer-specific mortality.[20] It remains to be seen whether this or other SNPs can predict the activity of abiraterone. Prospective incorporation of these biomarkers in ongoing studies (or alternatively, initiation of biomarker-driven trials) will be necessary to classify molecular predictors of response.

Identifying predictors of resistance will be of critical importance, as well. Recent data implicate the *TMPRSS2:ERG* fusion gene as a key regulator of expression of ETS family members, thereby driving aberrant cellular growth and proliferation.[21] Initial efforts have been made to characterize this moiety in the circulating tumor cells (CTCs) of patients receiving abiraterone therapy; its impact on efficacy is currently unclear.[22] Androgen receptor splice variants (ARVs) lacking a ligand-binding domain appear to be highly expressed in the setting of CRPC and theoretically could also modulate the response to abiraterone.[23] Several specific ARVs activate androgen receptor reporter genes in a ligand-independent fashion, promoting prostatic tumor growth in both *in vitro* and *in vivo* models. ARV expression appears to increase in the setting of androgen withdrawal and decrease with testosterone administration – given this property, it may be worthwhile to evaluate whether specific ARVs may confer a relative resistance to abiraterone therapy. While the phase III data for abiraterone is a milestone in mCRPC therapy, the fact remains that men with this disease are not cured. The challenge that lies ahead for abiraterone (amongst others cited herein) is to understand and overcome mechanisms of resistance.

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