Editorial

Abiraterone survival benefit is independent of pain, prostate-specific antigen and Gleason sum in men with chemo-naïve metastatic castration-resistant prostate cancer (analysis of COU-AA-302)

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Comment on: Miller K, Carles J, Gschwend JE, *et al.* The Phase 3 COU-AA-302 Study of AA Acetate Plus Prednisone in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Stratified Analysis Based on Pain, Prostate-specific Antigen, and Gleason Score. Eur Urol 2017. [Epub ahead of print].

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Advanced prostate cancer (PC), including metastatic castration-resistant prostate cancer (mCRPC) represents the lethal form of PC, yet remains largely dependent on androgen signaling (1). Abiraterone acetate (AA) is a steroid 17-hydroxylase/C17,20-lyase (CYP17) inhibitor targeting testicular, adrenal and intratumoral androgen production. AA is currently an integral part of the armamentarium for treatment of patients with advanced PC (2-5). The activity of the drug in the chemo-naive mCRPC setting was demonstrated in the hallmark phase III COU-AA-302 study (3). One thousand eighty-eight patients with mCRPC without clinically significant cancer-related symptoms and without prior exposure to chemotherapy were randomized 1:1 to receive either AA plus prednisone (AAP) or placebo plus prednisone (PP), ultimately demonstrating improvement in radiographic progression-free survival (rPFS) and overall survival (OS). Secondary endpoints included relevant clinical parameters including pain (pain time to opiate use for cancer-related pain, median time to decline in ECOG performance score by ≥1 point) and prostate-specific antigen [(PSA) time to PSA progression, ≥50% PSA decline from baseline] (3). Pain was assessed at baseline and at every visit to monitor any change in the baseline pain score at two consecutive visits by 30% or more, as measured by Brief Pain Inventory-Short Form (BPI-SF) (3). The OS benefit from AAP was derived in all pre-specified subgroups, including baseline ECOG PS 0 (HR =0.71), PS 1 (HR =0.86), baseline BPI-SF 0-1 (HR =0.71), BPI-SF 2-3 (HR =0.87), baseline PSA above (HR =0.71) and below median (not reached) (6). Also, AAP was superior in all secondary endpoints, including median time to opiate use for cancer-related pain (HR =0.69), median time to increase in pain (HR =0.69), median time to decline in ECOG performance score by ≥1 point (HR =0.82), median time to PSA progression (HR =0.49) and PSA decline ≥50% (HR =2.59) (3).

The prognostic value of pain or opiate use and PSA at primary diagnosis are well-established (7-9). Combined data from 3 randomized trials in mCRPC support an association between high pain score (≥17) assessed by BPI and a significantly shorter OS by 7.6 months compared to patients with low pain score (<17) (7). Baseline PSA and PSA decline in mCRPC patients were already reported by the first clinical trials of androgen-targeted therapies in the pre-AA era (e.g., flutamide, cyproterone) as important prognosticators of OS (8). In general, PSA and Gleason grade at initial diagnosis continue to carry prognostic weight, though less so with advanced staged CRPC than others such as lactate dehydrogenase (LDH) which together with other variables form the basis of prognostic nomograms (9,10). Other such as circulating tumor cell (CTC) count and quantity of plasma DNA may also be prognostic (11,12).

In an effort to further investigate whether these important prognosticators may result in any differential treatment effects across subgroups with respect to AA, Miller *et al.* conducted a post-hoc analysis of the COU-AA-302 study (13). After performing a univariate analysis, the investigators

identified tumor-related pain (BPI-SF score 2–3 *vs.* 0–1), PSA, Gleason score (<8 *vs.* ≥8), hemoglobin (Hb), LDH, ALP and age as independent prognosticators. Then, they proceeded with a stratified analysis of prostate cancer-specific variables including pain, PSA and Gleason (13). The COU-AA-302 study population was divided in two groups. Group 1 (n=264) included asymptomatic patients, without reported tumor-related pain (BPI-SF 0–1), with PSA <80 ng/mL, and GS <8. Group 2 (n=824) had patients with mild pain (BPI-SF2) and/or PSA ≥80 ng/mL and/or GS ≥8. Approximately half of the patients in each received AAP. Comparison of important time-to-event endpoints including OS, rPFS, time to chemotherapy, time to opiate use and treatment duration resulted in significant differences between AAP and PP subgroups favoring AAP (13). Thus, the authors concluded that both stratified groups, with or without presence of known prognostic PC-related factors, derived benefit from AAP (although the absolute benefit appeared to be smaller in group 2 patients).

It is important to highlight here that second or third line treatments post-AA may have also exerted an effect on OS. Indeed, 67% of patients from COU-AA-302 study went on to receive additional lines of treatment post-AA at the time of data cutoff (14). Additionally, a different prognostic model was developed by the investigators of COU-AA-302 to predict rPFS (15). They reported 3 prognostic groups (good, intermediate, and poor with median rPFS of 27.6, 16.6, and 8.3 months respectively) and included patient-related predictors (LDH, Hb) and a different PSA cut-off of 39.5 ng/mL (15).

Taking into account the limitations discussed above, the stratified analysis performed by Miller *et al.* (13) further emphasizes the key role that targeting the AR pathway still holds in the treatment of prostate cancer and corroborates the impact of AA on outcome improvement in mCRPC. Yet, the study demonstrated limitations of the more traditional clinical markers to recognize those patients more likely to respond to treatment, i.e., we are still lacking predictive factors. Some post-treatment factors may be associated with outcome, but are not available prior to treatment selection. For example, not simply the baseline pretreatment PSA but the actual PSA changes [PSA nadir, PSA response rate (≥30%, 50%, and 90%)] and time to PSA progression were associated with OS in the combined patient population of COU-AA-301 and COU-AA-302 (16). Moreover, other measurable laboratory parameters such as CTCs or chromogranin and neuron-specific enolase may add prognostic information in patients receiving AA and post-treatment changes (at least for CTC count by CellSearch) are also prognostic (17,18).

In light of the eventual development of drug resistance to androgen receptor (AR)-targeting drugs (AA and enzalutamide) and chemotherapy, it is becoming increasingly important to identify new predictors of resistance to these agents. Several attempts have been made to clinically validate markers able to early predict response or resistance to treatment, for both hormone therapies and taxanes (19). In fact, this need is not only confined to mCRPC patients but also extends to the hormone-sensitive setting, given evidence for use of AA in combination with frontline ADT (4,5).

Numerous molecular mechanisms have been identified *in vitro* to affect AA efficacy in suppressing AR signaling, with some of those also confirmed in clinical studies (20). As AR remains the main driver of PC progression, any alteration of its pathway could play a central role in the onset of AA resistance. Somatic AR gene amplifications and mutations are commonly observed aberrations in patients with CRPC and have been indicated as potential mechanisms supporting tumor progression during androgen deprivation therapy (ADT) (20). Even though AR gain or amplification are not frequent events in untreated PC, these alterations can be found in up to 45% of CRPC patients progressing after AR-targeting drug treatment and may be associated with resistance to AR-signaling inhibitors (21). Interestingly, AA exposure can aberrantly induce progesterone-dependent AR activation in prostate cancer harboring AR mutations; it has been indeed shown that, when AA blocks its target CYP17A, the consequent increase in intracellular progesterone levels fuels AR pathway activation in the presence of T877A or T878A AR mutations, which increase AR affinity for progesterone, leading to AA resistance (22). Additionally, the expression of transcriptionally active AR splice variants (AR-Vs) has been investigated. As they retain the trans-activating N-terminal domain but lack the C-terminal ligand-binding domain of the receptor, AR variants maintain transcriptional activity in a ligand-independent fashion; thus, they have been implicated in mediating prostate cancer progression in castrate conditions. The presence of such variants has been mechanistically linked to resistance to AR-targeting drugs. For example, the detection of AR-V7 at the mRNA or protein level has been associated with lack of response to treatment in patients receiving AA or enzalutamide (23). External validation of this CTC-based mRNA assay and others assessing AR-V7 in the setting of abiraterone/enzalutamide and taxane chemotherapy is

anticipated [NCT02269982]. More recently, the ligand-independent AR-V9 has also been described and high levels of AR-V9 expression was retrospectively associated with primary resistance to AA in CRPC (24). However, a more extensive clinical validation of the role of this splice variant in predicting resistance to AA and other AR-targeting drugs is warranted.

Aberrations in pathways other than AR have also been implicated in AA resistance. Such an example involves the loss of the tumor suppressor phosphatase and tensin homolog (PTEN), which is associated with shorter time on AA and shorter OS (25). In contrast, the ETS-related gene (ERG) transcriptional factor, which is found overexpressed in about 50% of prostate cancer consequently to the TMPRSS2-ERG gene fusion, predicts sensitivity to AA and greater improvement in rPFS compared to cancer with no ERG fusion (26,27). As we gain increased understanding of mechanisms of primary or early clinical resistance and develop biomarkers with clinical utility, clinicians will be better able to choose amongst our growing treatment armamentarium for advanced prostate cancer.

In conclusion, AA is a key drug for treatment of patients with advanced prostate cancer. While AA has consistently demonstrated a significant benefit across patients with different prognostic factors, it is important to recognize the limitations and heterogeneity of different characteristics which may give prognostic, but rarely predictive information. We encourage additional research to simultaneously better understand the biology underlying AA response and resistance and develop predictive biomarkers to further improve patient outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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