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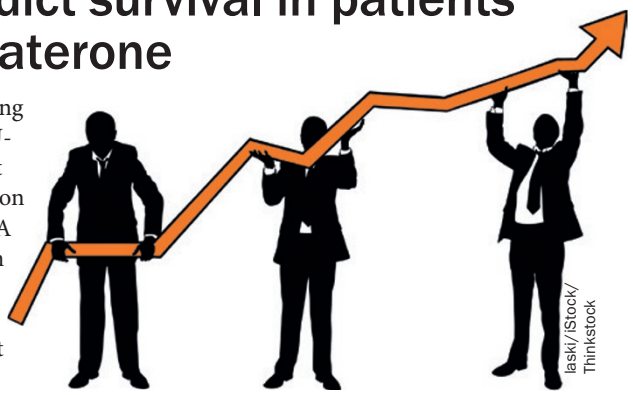
PROSTATE CANCER

# PSA kinetics predict survival in patients treated with abiraterone



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A biomarker-survival model study using data from the COU-AA-301 and COU-AA-302 phase III trials has shown that overall survival outcomes for patients on abiraterone can be predicted using PSA kinetics, in a recent paper published in *Clinical Cancer Research*.

Prostate cancer, particularly once it becomes metastatic, is difficult to treat and monitor. Abiraterone acetate, the prodrug of abiraterone, which irreversibly inhibits the CYP17 enzyme, is becoming a widely used therapeutic option for men with metastatic castration-resistant prostate cancer (mCRPC), and improves overall survival and radiographic progression-free survival in both chemotherapy-treated and chemotherapy-naive men, as shown in the COU-AA-301 and COU-AA-302 trials, respectively. The mechanism of action of abiraterone, in conjunction with the relationship between PSA kinetics and androgen receptor (AR) activity, means that the data contained in the COU-AA-301 and COU-AA-302 offer an excellent opportunity to use modelling techniques to understand the connection between PSA kinetics and survival in men with mCRPC receiving abiraterone.

Xu and colleagues constructed a longitudinal PSA kinetic model to describe PSA kinetics, abiraterone's antitumour effects, and treatment resistance after abiraterone therapy. Survival models were also constructed, with univariate Cox models developed for individual model-predicted PSA kinetic end points, and Prentice criteria for surrogacy were evaluated.

Diagnostic plot of the observed and predicted PSA concentrations for individual subjects showed that the PSA kinetic model closely adhered to individual PSA concentration. Using this model, the estimated effect of abiraterone plus prednisone compared with prednisone alone (which was used as the control group in both trials) was a 1.21-fold increase in PSA kinetics in chemotherapy-pretreated patients and a 1.44-fold increase in chemotherapy-naive men. Model-predicted PSA summary end points were also investigated, and all were observed to be greater in patients who had received abiraterone in both chemotherapy-naive and chemotherapy-treated men. "All investigated PSA measures (that is, PSA nadir, PSA response rate [≥30%, 50%, and 90%], time to PSA progression, and PSADT) were significantly associated with overall survival ($P$<0.0001)," the authors told *Nature Reviews Urology*. "A strong correlation was also observed between PSA and radiographic progression-free survival ($P$<0.0001)."

In fact, model-predicted post-treatment PSADT had the strongest association with overall survival in chemotherapy-treated patients, and was in the top three most strongly associated PSA measures in the chemotherapy-naive patients.

Overall survival is considered the gold standard outcome to assess the effect of cancer therapies, but its use its limited by the need for long follow-up durations and interference from other anticancer treatments. Models that can accurately predict overall survival are, therefore, highly valuable. The mechanism of action of abiraterone—a disruption of AR-signalling—makes PSA a logical biomarker to monitor its effect, and this study suggests that PSA is an accurate predictor regardless of whether a patient received abiraterone before or after chemotherapy. The authors assert that PSA kinetics models might be useful for predicting the treatment effect of other prostate cancer agents that exert their antitumour activity through PSA-dependent mechanisms.

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**Original article** Xu, X. S. *et al.* Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-14-1549