Nature Reviews Urology **10**, 1 (2013); published online 27 November 2012; doi:10.1038/nrurol.2012.232

PROSTATE CANCER

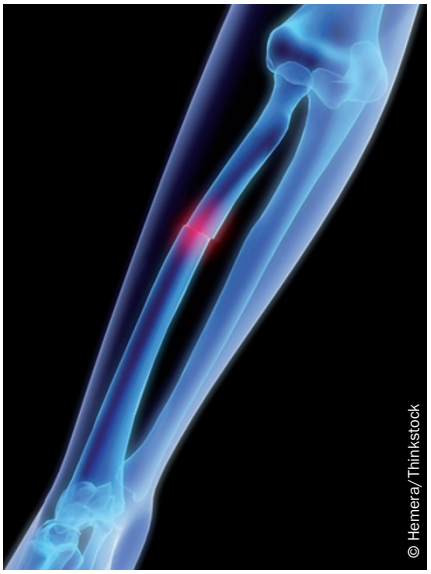
Abiraterone benefit extends to bone-related symptoms

Abiraterone acetate not only improves survival, but also provides pain relief and delays the occurrence of skeletal-related events, compared with placebo, in patients with metastatic castration-resistant prostate cancer (CRPC), according to new analysis of the COU-AA-301 trial published in *The Lancet Oncology*.

COU-AA-301 is the phase III randomized placebo-controlled trial that led the FDA to approve abiraterone acetate as a second-line treatment for men with metastatic CRPC refractory to docetaxel in April 2011. Primary survival outcomes of COU-AA-301 were published in May 2011, revealing a 4-month survival advantage for abiraterone acetate. Now, the trial investigators, led by Howard Scher and Johann de Bono, have turned their attention to the quality-of-life effects of abiraterone acetate by analysing the bone-related outcomes of patients enrolled in COU-AA-301.

Pain parameters (intensity and interference with daily life) and skeletal data were prospectively collected from the 1,195 patients accrued to the trial, who were randomized to receive 28-day treatment cycles of either abiraterone acetate or placebo, in combination with prednisone, until they experienced disease progression. Pain was assessed using the Brief Pain Inventory-Short Form questionnaire at baseline, day 15 of the first treatment cycle, and day 1 of each subsequent treatment cycle. Patients underwent bone imaging at baseline, day 1 of every third cycle and at treatment discontinuation. Radiography was used to assess pathological fractures and spinal cord compression when needed.

Palliation of pain was only evaluated in men with clinically significant pain at baseline; approximately 40% of men in each treatment group reported significant pain intensity at randomization, and about 25% reported significant interference with daily activities. Over the course of their treatment, significantly more men in the abiraterone acetate plus prednisone group



experienced pain relief than those who received placebo plus prednisone, in terms of both intensity (45.0% versus 28.8%; $P = 0.0005$) and interference (60.1% versus 38.0%; $P = 0.0002$). Moreover, median time to palliation was shorter and median duration of relief was longer for those patients who received abiraterone acetate.

In the overall population, time to first occurrence of a skeletal-related event—defined as pathological fracture, spinal cord compression, palliative radiation to bone, or bone surgery—was significantly longer in men who received abiraterone acetate than placebo (median delay of 4.7 months; HR 0.615, 95% CI 0.478–0.791; $P = 0.0001$). However, bisphosphonate treatment was not controlled for, and 44.9% of patients in the active treatment group and 50.0% of controls reported bisphosphonate use during the study.

The implications of these findings are twofold. Firstly, the alleviation of bone-related symptoms makes abiraterone acetate an attractive choice for men with metastatic CRPC who report bone pain. Secondly, the efficacy of abiraterone acetate in this context provides some insight into the mechanisms of prostate cancer progression. Abiraterone acetate blocks CYP17, a key enzyme in androgen production. Thus, these new data support the hypothesis that androgen signalling is involved in bone progression of CRPC.

Although it might seem obvious for a drug that improves CRPC survival to also ameliorate bone symptoms, and vice versa, this isn't always the case. Sipuleucel-T, for example, has demonstrated a survival advantage in men with asymptomatic CRPC but palliative effects are yet to be established. On the other hand, bone-targeting agents denosumab and zoledronate, both well-known for their ability to prevent skeletal-related events, are not associated with improved survival.

Clearly, drugs that provide benefit to patients in terms of both survival and bone-related symptoms are much needed, and abiraterone acetate can now join enzalutamide and radium-223 chloride in this category.

Obviously this study is not without its limitations, and the previously mentioned uncontrolled bisphosphonate use is one possible confounder. Moreover, the lack of information regarding occurrence of skeletal-related events before trial enrolment and infrequent bone scanning should also be taken into account.

The promising results of this study will undoubtedly spur other researchers to investigate pain relief and skeletal-related events in CRPC drug trials. The authors express their hope that this study will persuade others that pain palliation deserves a prominent role in future trial design. Finally, given the different targets of abiraterone acetate (androgen signalling) and radium-223 chloride (the bone microenvironment), the authors suggest a future study of combined treatment in men with metastatic CRPC might be on the cards.

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Original article Logothetis, C. J. *et al.* Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol.* doi:10.1016/S1470-2045(12)70473-4