high-risk metastatic prostate cancer who had not received hormone therapy. At a median follow-up of 30.4 months, they confirmed the significant effect of abiraterone plus prednisone in combination with androgen-deprivation therapy. The median rate of overall survival was not reached among patients in the abiraterone group as compared with 34.7 months among those in the placebo group (hazard ratio for death, 0.62; 95% confidence interval, 0.51 to 0.76; P<0.001). The STAMPEDE trial showed similar results.

The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) showed a similar outcome with the use of six cycles of docetaxel in combination with androgen-deprivation therapy, and docetaxel is very affordable as compared with abiraterone plus androgen-deprivation therapy.\(^1\) Comparative and cost-effective studies should be conducted to define the best systemic therapy for patients with metastatic prostate cancer who have not received hormone therapy.

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**DR. JAMES AND COLLEAGUES REPLY:** In response to de Bono and colleagues, who ask about the development of a clinically meaningful early surrogate end point in patients with prostate cancer who have not received hormone therapy; this has been an unmet need. The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) collaboration has addressed this issue in patients with nonmetastatic disease;\(^2\) the ICECaP collaboration is now expanding to include men with metastatic (M1) disease.

They also ask whether survival gains observed in the STAMPEDE and LATITUDE trials were boosted by inadequate access to abiraterone and enzalutamide on relapse. STAMPEDE was an open-label trial in which treatments in patients with disease that had relapsed were determined by the responsible clinician. During the trial, abiraterone and enzalutamide were widely available, as were docetaxel, cabazitaxel, and radium-223. These “life-prolonging” agents have similar effects on survival among patients with relapsed prostate cancer; there is no agreed-upon single standard of care.\(^2\) Among the patients in the control group (i.e., patients who received androgen-deprivation therapy alone) in the STAMPEDE trial who died of prostate cancer, 74% explicitly reported that they had received one or more of these five therapies. Data on second-, third-, and fourth-line treatments are increasingly difficult to collect and thus are underreported, so true rates of exposure to these therapies will be higher than 74%. The double-blind, placebo-controlled LATITUDE trial produced strikingly similar outcomes with different patterns of care after relapse; this suggests that differing patterns of care after relapse between the STAMPEDE and LATITUDE trials were not important drivers of differences in survival.

Furthermore, among patients with relapsed disease who had not received previous chemotherapy and who received abiraterone in the COU-AA-302 study, the median progression-free survival was approximately 16.5 months,\(^3\) and the median time to treatment failure in the control group of patients with M1 disease in the STAMPEDE trial was approximately 11 months, so the estimated time to abiraterone failure was 27.5 months. In comparison, the median failure-free survival with first-line abiraterone among patients with metastatic disease in the STAMPEDE trial was approximately 54 months; this suggests that a crossover strategy would not have yielded a different outcome.

In response to Tannock: drug development is more than chemical synthesis. Much value lies in the intellectual property in clinical development, which is costly and lengthy. Drug development depends on investment generating sufficient return for investors and inventors. The U.S. patent extension is sub judice. Drug pricing is complex, and the U.S. headline price is far higher than the price paid elsewhere. Affordability is thus a function of the need for health care systems and payers to collaborate with drug developers to ensure an active, continual pipeline while ensur-
ing value for all. As highlighted by de Bono et al., more robust, surrogate end points and new trial designs (as used in the STAMPEDE trial) can help speed trial completion and thereby reduce costs for all concerned.

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**Drs. Fizazi and Chi Reply:** The phase 3 LATITUDE trial showed an improved outcome, including prolonged survival, when abiraterone and prednisone were combined with androgen-deprivation therapy in men with newly diagnosed metastatic prostate cancer.

In their letter, de Bono and colleagues question the control regimen used in the LATITUDE trial, which consisted of androgen-deprivation therapy alone, followed in cases of cancer progression by drugs recommended for castration-resistant prostate cancer and used according to the investigators’ decision. However, although six drugs have been shown to improve survival among men with castration-resistant prostate cancer, no clear guidance for their use is available. Moreover, many physicians may prefer the use of a taxane rather than a drug targeted to the androgen-receptor axis such as abiraterone or enzalutamide at the onset of progression in men in whom castration-resistant prostate cancer may quickly develop. Thus, a mandatory crossover to abiraterone in our trial may have been challenging and perhaps in some cases clinically inadequate. Finally, the LATITUDE trial is not an exception among its kind: data are limited from randomized trials in advanced prostate cancer that have used a systematic crossover of the experimental drug in the control group. Of note, in the LATITUDE trial, more patients in the placebo group than in the abiraterone group received at least one life-prolonging therapy after they had disease progression (246 vs. 125 patients [41% vs. 21%], respectively). This suggests that the survival benefit observed in the experimental group was truly related to the initial use of abiraterone, not to active drugs used after disease progression.

Tannock, as well as Ismaili and Guessous, emphasize the financial cost of abiraterone, and they respectively advocate for a reduction of price or comparison with docetaxel (a generic drug). We agree that drug pricing should generally be adapted so that most patients can benefit worldwide, and this opinion is not restricted specifically to abiraterone. Regarding the comparison with docetaxel, although no direct comparison with a randomized trial is available, indirect comparisons with the use of Bayesian network analysis are ongoing, and we agree that cost-effectiveness studies will be important to perform. Consideration should be given to differences between the two regimens (i.e., androgen-deprivation therapy plus docetaxel and androgen-deprivation therapy plus abiraterone) with respect to toxic effects and the potential effect on quality of life. An important question will be whether abiraterone also improves outcomes in men receiving androgen-deprivation therapy plus docetaxel as their standard of care, and this is currently being tested in the PEACE1 trial (ClinicalTrials.gov number, NCT01957436).

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Since publication of their article, the authors report no further potential conflict of interest.