agree that the use of IdeS in patients with strong cytotoxic antibodies needs to be approached carefully. The high rate of delayed graft function in the U.S. cohort is similar to what we see in our recipients of deceased donor kidneys. Delayed graft function is unlikely to be due to IdeS, since it was not seen in the Swedish population, which involved donors with low cold ischemia times and machine perfusion.

We performed renal biopsies in four patients during the first week after transplantation. All the biopsy specimens showed mild tubular injury with no microvascular inflammation and no C4d staining. In addition, no evidence of IgG fragments was seen in the glomeruli or tubules. Signaling by $F(ab')_2$ fragments of donor-specific antibodies has been described.[1] Using an in vitro model of neuromyelitis optica in which antibodies to the autoantigen aquaporin-4 (AQP4) were cleaved by IdeS, Tradtrantip et al.[2] found that $F(ab')_2$ fragments of anti-AQP4 binding to AQP4-positive cells protected cells from antibody-dependent cellular and complement-mediated cytotoxic effects by intact anti-AQP4 IgG. The sample size in our study is too small to stratify patients according to the estimated glomerular filtration rate on the basis of chronic kidney disease status. We agree that larger studies of IdeS with the use of protocols to block antibody rebound are critical.

Goldstein believes that we have overstated the degree to which sensitization impedes the transplantation of kidneys from deceased donors. The assertion that sensitized patients undergo transplantation at rates similar to those among nonsensitized patients is not accurate. Although the new kidney allocation system has dramatically increased transplantation rates among candidates with a calculated panel-reactive antibody level of 100%, a substantial percentage (40 to 47%) of these candidates underwent transplantation across positive donor-specific antibodies and flow-cytometric cross-match barriers after completing desensitization.[3] The rate of transplantation of a deceased donor kidney among candidates with a calculated panel-reactive antibody level of 100% increased (from 2.4% to 13.4%) after the implementation of the kidney allocation system. However, recent data show that the transplantation rate among these candidates has decreased to 9.4%. The transplantation rate among candidates with a calculated panel-reactive antibody level of 95 to 98% is 3.1%.[4] For Eurotransplant, a suitable donor cannot be found for a considerable percentage (approximately 35%) of highly HLA-sensitized patients (http://cordis.europa.eu/result/rcn/181463_en.html). In that circumstance, desensitization is the only option to increase transplantation rates.

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

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Abiraterone in Metastatic Prostate Cancer

TO THE EDITOR: Fizazi et al. (July 27 issue)[1] report on the LATITUDE trial, and in the same issue, James et al.[2] report on the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial. These phase 3 trials involving a total of more than 3000 men with advanced prostate cancer were designed after abiraterone was proved to prolong survival

among patients with advanced prostate cancer. Before these trials, the standard of care for patients with advanced prostate cancer included sequential androgen suppression with various life-prolonging therapies (e.g., taxanes, abiraterone, or enzalutamide).

However, the control regimens in the STAMPEDE and LATITUDE trials were not designed to include the current sequential standard of care with life-prolonging crossover treatments; these treatments were not specified in the protocols (available with the full text of the articles at NEJM.org). This is critical, since the majority of men in the control groups in the STAMPEDE and LATITUDE trials died without exposure to abiraterone or enzalutamide. Thus, the drugs used in these control groups were inconsistent with current prevailing standards of care. This has implications for the conclusions of the trials and raises questions regarding whether or not there was a benefit for all trial participants.

Discussions between patients and physicians regarding the results of these trials should be made in the context of the above considerations. Physicians must reflect on the urgent need to better define and use surrogate end points so that death is not needed to conclude that a regimen is active.

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Dr. de Bono reports holding a patent for abiraterone and receiving advisory board fees from AstraZeneca, Sanofi-Aventis, Astellas Pharma, Janssen, Pfizer, Genentech, and GlaxoSmithKline; and Dr. Sartor, receiving consulting fees and grant support for serving as a clinical trial investigator from Janssen, Sanofi-Aventis, Bayer, and Dendreon and consulting fees from Medivation and Pfizer. No other potential conflict of interest relevant to this letter was reported.

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2. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338-51.

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TO THE EDITOR: The STAMPEDE and LATITUDE trials show that abiraterone improved survival substantially among men with metastatic prostate cancer when this drug was added to standard androgen-deprivation therapy. Abiraterone has minimal toxic effects and would benefit such men worldwide, but it is available to only a minority of patients. The monthly price of abiraterone at the Food and Drug Administration–approved dose of 1000 mg per day (after an overnight fast) is approximately $10,000 in the United States; this is unaffordable in middle-income and lower-income countries.

The price of abiraterone bears no relationship to the minimal cost of production. Abiraterone was developed and first patented at the Institute of Cancer Research in the United Kingdom in the early 1990s. Janssen markets the drug and has an extended patent based on a questionable claim for combined administration with prednisone. A recent study points to ways to increase the availability of abiraterone by suggesting that the administration of 250 mg per day after consumption of a low-fat meal may be as effective as the higher dose (after an overnight fast)[1] and that full-dose abiraterone is available in India for approximately $450 per month. Given that the drug was developed 25 years ago in an academic center, the high price is unacceptable. We recommend that oncologists lobby to make abiraterone available to all patients who might benefit, just as retroviral drugs are available for patients with AIDS.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Fizazi et al. suggest that abiraterone plus prednisone in combination with standard androgen-deprivation therapy significantly improved outcomes among patients with

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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No potential conflict of interest relevant to this letter was reported.

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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[1]; 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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Since publication of their article, the authors report no further potential conflict of interest.

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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.[1] 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.[2] 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.[3,4] 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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Migraine

TO THE EDITOR: In the discussion of preventive therapy for migraines, Charles (Aug. 10 issue)[1] did not include aspirin as an effective option. Several large, randomized, double-blind, placebo-controlled trials, including the Physicians' Health Study,[2] have reported that the regular use of low-dose aspirin is effective in migraine prevention. A recent systematic review of studies on migraine prophylaxis with aspirin confirmed that regular use of low-dose aspirin can reduce the frequency of migraine.[3] A comparison study of aspirin and metoprolol for migraine prevention reported reductions in migraine frequency in both groups, with the metoprolol group having a greater response (42.5%, vs. 29.6% in the aspirin group) but also having more medication-related side effects than the aspirin group.[4] Another recent review of drugs for migraine also neglected to discuss the effectiveness of aspirin in prophylaxis.[5] Given its documented effectiveness, low side-effect profile (especially in the young), and low cost, aspirin should not be overlooked as a useful means of migraine prevention.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Langland points to studies indicating the potential efficacy of acetylsalicylic acid (aspirin) as preventive therapy for migraine. Although these studies do report that acetylsalicylic acid, at a dose of 325 mg, is of modest benefit for migraine prevention, the data are not sufficient to warrant the highest level of recommendation in any of the major guidelines.[1-3] Nonetheless, it is reasonable to consider acetylsalicylic acid as a preventive approach to migraine, particularly in patients who have other conditions for which daily acetylsalicylic acid may be beneficial. A number of other treatments fall into this category — that is, those for which there is some evidence of efficacy but for which there is neither sufficient evidence nor expert consensus to warrant the highest level of recommendation. These treatments include other nonsteroidal antiinflammatory medications,[1] flunarizine, gabapentin, venlafaxine, verapamil,[2-4] and behavioral therapies,[5] among multiple others. As is the case with acetylsalicylic acid, these treatments may be considered as migraine-preventive therapies in patients with other coexisting conditions for which the treatments are indicated or in patients for whom first-line approaches are ineffective or have unacceptable side effects.

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Since publication of his article, the author reports no further potential conflict of interest.

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