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(Article begins on next page)
Enzalutamide in Prostate Cancer after Chemotherapy

TO THE EDITOR: In the randomized trial reported by Scher et al. (Sept. 27 issue), the administration of enzalutamide, an androgen-receptor–signaling inhibitor, was associated with an increased incidence of headache, as compared with placebo, in patients with castration-resistant prostate cancer. Androgens are implicated in the pathogenesis of migraine; thus, it is important to understand whether the headache associated with enzalutamide could be classified as migraine. Moreover, a deeper understanding of the pathophysiology of this side effect is clinically relevant, since a relationship between migraine and the presence of either hot flashes or seizures has been described previously. Migraine and epilepsy have pathophysiological characteristics in common, so patients who have migraine during enzalutamide therapy may be at increased risk for seizures. Notably, headache was not reported as a clinically relevant symptom in patients with castration-resistant prostate cancer who received abiraterone, a drug that deeply reduces circulating androgen levels. Abiraterone was administered in association with prednisone, and glucocorticoids are efficacious in preventing migraine. It would be interesting to know whether glucocorticoids were used in the management of enzalutamide-induced headache and whether they were effective.

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Dr. Berruti reports being an advisory board member for, and receiving consulting fees from, Astellas Pharma and Janssen Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.


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THE AUTHORS REPLY: In AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100), data on the adverse events of
migraine and headache were collected separately. Of the 800 patients treated with enzalutamide, 3 (0.4%) were reported to have had a migraine. Headaches were reported in 93 patients treated with enzalutamide (11.6%) and in 22 of the 399 patients treated with placebo (5.5%). In the enzalutamide group, the majority of reports were for grade 1 headache that did not require treatment. No patient was treated for headache with glucocorticoids. One patient reporting seizure in AFFIRM reported a headache 5 months before the report of seizure.

Berruti et al. state that headaches were not reported as a relevant symptom in patients receiving abiraterone acetate plus prednisone in a recent phase 3 study. However, the clinical review of abiraterone acetate by the Food and Drug Administration (new drug application number, 202379) reported a similar frequency of headache in the two study groups (11.9% of patients in the abiraterone-plus-prednisone group and 10.7% of those in the placebo-plus-prednisone group).

Overall, these data do not support the suggestion by Berruti et al. that the headaches observed in the enzalutamide study reflect migraines, nor that patients who had a headache during treatment with enzalutamide are at increased risk for seizure.

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


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**Understanding Low Sugar from NICE-SUGAR**

**TO THE EDITOR:** In his editorial about the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, Hirsch (Sept. 20 issue) declares, “For surgical patients, especially those who have undergone cardiac procedures, hospitals that can safely achieve lower targets should do so.” No justification for this statement is provided. Concerns exist regarding the generalizability of studies of glycemic control in other populations of patients treated in intensive care units (ICUs) that have shown either harm or no benefit and regarding both the generalizability and applicability of studies that have shown benefit. Accordingly, the effect of maintaining the blood sugar levels of surgical patients admitted to the ICU below those of the control group in the NICE-SUGAR study remains uncertain. We believe the targeting of blood glucose levels below that of the control group in this study should occur only in the context of well-designed clinical trials. To do otherwise exposes surgical patients admitted to the ICU to a therapy of uncertain benefit and that is associated with harm in other ICU patient populations.

It also promotes the inefficient use of valuable health care resources at a time when the Journal is fostering debate around this challenging issue.

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**THE EDITORIALIST REPLIES:** French and McGain bring up an important point. The most recent