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Letter to the Editor

Reply to Brandon A. Mahal, Anthony V. D'Amico, and Paul L. Nguyen's Letter to the Editor re: Neal D. Shore, Fred Saad, Michael S. Cookson, et al. Oral Relugolix for Androgen Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med 2020;382:2187–96

We agree with Mahal and colleagues that there is considerable imprecision in estimates of the duration of androgen suppression when used in conjunction with radiotherapy. This exists because of the variable duration of testosterone suppression after cessation of parenteral androgen suppression using luteinizing hormone–releasing hormone (LHRH) agonists. This is particularly marked with longer durations of treatment (≥6 mo), use of ≥3-mo depot preparations, and patient-related factors including age and pretreatment testosterone levels [1].

European and American clinical practice guidelines recommend 4–6 mo and 18–36 mo of androgen deprivation therapy (ADT) for patients with intermediate-risk disease and high-risk advanced localized disease, respectively [2–6]. There is no clear evidence that the duration of castration beyond the actual timeframe of therapy is needed or linked to the outcomes observed in clinical trials [7]. In fact, biochemical recurrence in the setting of more rapid testosterone recovery may earlier identify patients for whom radiotherapy was not curative.

Relugolix, a once-daily oral gonadotropin-releasing hormone (GnRH) antagonist, has yielded reliable and rapid recovery of testosterone levels compared to both 3-mo injections of leuprolide [8] and monthly injections of degarelix [9]. The faster testosterone recovery improves the precision of treatment, importantly reducing the risk of testosterone suppression overtreatment. Studies of 2- to 3-yr periods of ADT using relugolix in patients with high-grade and locally advanced cancers will be informative and may demonstrate mitigation of cardiovascular toxicity and other undesirable castration-related side effects. In the end, it will be the patient and the doctor who must choose between the certainty of more rapid testosterone recovery and a theoretical detriment, just as they have choices to make, for example, between the dose of radiation, quality of life, and improvement in survival [10].

Regarding major adverse cardiovascular events (MACE), the MACE incidence on ADT versus ADT combined with antiandrogen use for flare protection or prolonged combined androgen blockade is not known, although it has been explored in an observational study that suggested that antiandrogen use is not responsible for the increase in MACE observed with LHRH agonist treatment [11]. In a randomized trial involving 80 men with advanced prostate cancer and preexisting cardiovascular disease, Margel and colleagues [12] found that 20% of those treated with an LHRH agonist every 3 mo had a MACE, compared with 3% of those treated with degarelix ($p = 0.01$). These results are very similar to the MACE incidence observed in the HERO study in the subgroup of men with a history of cardiovascular events (3.6% in the relugolix group and 17.8% in the leuprolide group). Of the patients experiencing MACE in the HERO study, no patient on leuprolide and one patient on relugolix received an antiandrogen (bicalutamide, flutamide, or enzalutamide) on study before or at the time of the MACE. Overall, 11.5% of patients in HERO received at least one antiandrogen, 27.9% in the leuprolide group and 3.4% in the relugolix group. The use of an antiandrogen did not confound the differences in MACE observed between groups in the HERO study.

Conflicts of interest: Neal D. Shore has received grants and personal fees from Amgen, Astellas, AstraZeneca, Bayer, Dendreon, Ferring, Janssen, Merck, Pfizer, Sanofi-Genzyme, Tolmar, BMS, Myovant, and Nymox. Bertrand Tombal has received grants from Myovant, and grants and personal fees from Astellas, Bayer, Janssen, Ferring, and Sanofi. David Dearnaley is employed by the Institute of Cancer Research (ICR), which receives royalty income from abiraterone. He receives a share of this income through the ICR Rewards to Discoverers scheme. He holds patent EP1933709B1 for a location and stabilization device in radiotherapy.

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Neal D. Shore[a,*]
David Dearnaley[b]
Bertrand Tombal[c]

[a]*Carolina Urologic Research Center, Myrtle Beach, SC, USA*
[b]*The Institute of Cancer Research and Royal Marsden Hospital, London, UK*
[c]*Service d'Urologie, Cliniques Universitaires Saint Luc, Brussels, Belgium*

*Corresponding author. Carolina Urologic Research Center, 823 82nd Parkway, Myrtle Beach, SC 29572, USA.
E-mail address: nshore@gsuro.com (N.D. Shore).

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