New-Generation Hormone Therapies in Nonmetastatic Castration-Resistant Prostate Cancer: Why, Who, When

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The use of a novel generation of androgen receptor's inhibitors has dramatically changed the management of metastatic castration-resistant prostate cancer (CRPC).[1] Conversely, nonmetastatic CRPC has been considered a condition without any active drug for several years. Recently both apalutamide, a nonsteroidal anti-androgen agent, and enzalutamide, an inhibitor of the androgen receptor, have shown to prolong the time of development of metastatic disease in patients with nonmetastatic CRPC in the randomized phase 3 Spartan and Prosper trials.[2,3] However, although the efficacy of apalutamide and enzalutamide was clearly demonstrated against placebo, there is a need to better define candidates to receive a novel antiandrogen therapy in the setting of nonmetastatic CRPC. Therefore, we aimed to discover possible predictors of efficacy when a novel antiandrogen therapy is administered to patients with nonmetastatic CRPC.

Pooled analysis revealed that these novel antiandrogen therapies showed significantly improved metastasis-free survival (hazard ratio [HR] = 0.29; 95% confidence interval [CI], 0.25-0.33; $P < .00001$, $I^2 = 0$; Figure 1A). In addition, the analysis focusing on survival (Figure 1B) showed that the use of enzalutamide and apalutamide was associated with a greater reduction of risk of death (HR = 0.76; 95% CI, 0.59-0.97; $P = .03$, $I^2 = 0$). To discover the best candidate to receive novel antiandrogen therapy in non-metastatic CRPC, a subgroup analysis was performed to highlight any differences between studies according prostate-specific antigen (PSA) doubling time (> 6 vs. < 6 months), Eastern Cooperative Oncology Group performance status (ECOG PS) (1 vs. 0), and concomitant use of bone-targeting agent (yes vs. no). These 3 characteristics were chosen because they are all reported in the 2 randomized phase 3 studies.

The pooled analysis according PSA doubling time (> 6 vs. < 6 months) revealed that metastasis-free survival was significantly improved to a greater extent in men with PSA doubling time < 6 months (HR = 0.28; 95% CI, 0.24-0.33; $P < .00001$, I^2: 0% Figure 1C) compared to PSA doubling time > 6 months (HR = 0.32; 95% CI, 0.24-0.44; $P < .00001$, I^2: 0% Figure 1C). The pooled analysis according ECOG PS (1 vs. 0) revealed that metastasis-free survival was significantly improved to a greater extent in men with ECOG PS 0 (HR = 0.27; 95% CI, 0.23-0.32; $P < .00001$, I^2: 0% Figure 1D) compared to ECOG PS 1 (HR = 0.41; 95% CI, 0.31-0.55; $P < .00001$, I^2: 0% Figure 1D). Finally, the pooled analysis addressing concomitant use of bone-targeted agents (yes vs. no) revealed that metastasis-free survival was significantly improved to a greater extent in men who received no bone-targeted agents (HR = 0.29; 95% CI, 0.25-0.34; $P < .00001$, I^2:0% Figure 1E) compared to men who had received bone-targeted agents (HR = 0.40; 95% CI, 0.26-0.33; $P < .0001$, I^2: 0% Figure 1E).

In conclusion, although this analysis foregrounds the limitations of the literature rather than addressing individual patients' data via a meta-analysis and therefore definitive conclusions need to be considered carefully, our data show that the use of enzalutamide or apalutamide seems to better reduce the risk of metastasis in patients with a PSA doubling time of < 6 months, ECOG PS of 0, and no concomitant use of bone-targeted agents. These last 2 characteristics were involved in the best reduction of risk of developing metastasis. However, these data will require further evaluation in prospective randomized clinical trials.

Disclosure

The authors have stated that they have no conflict of interest.

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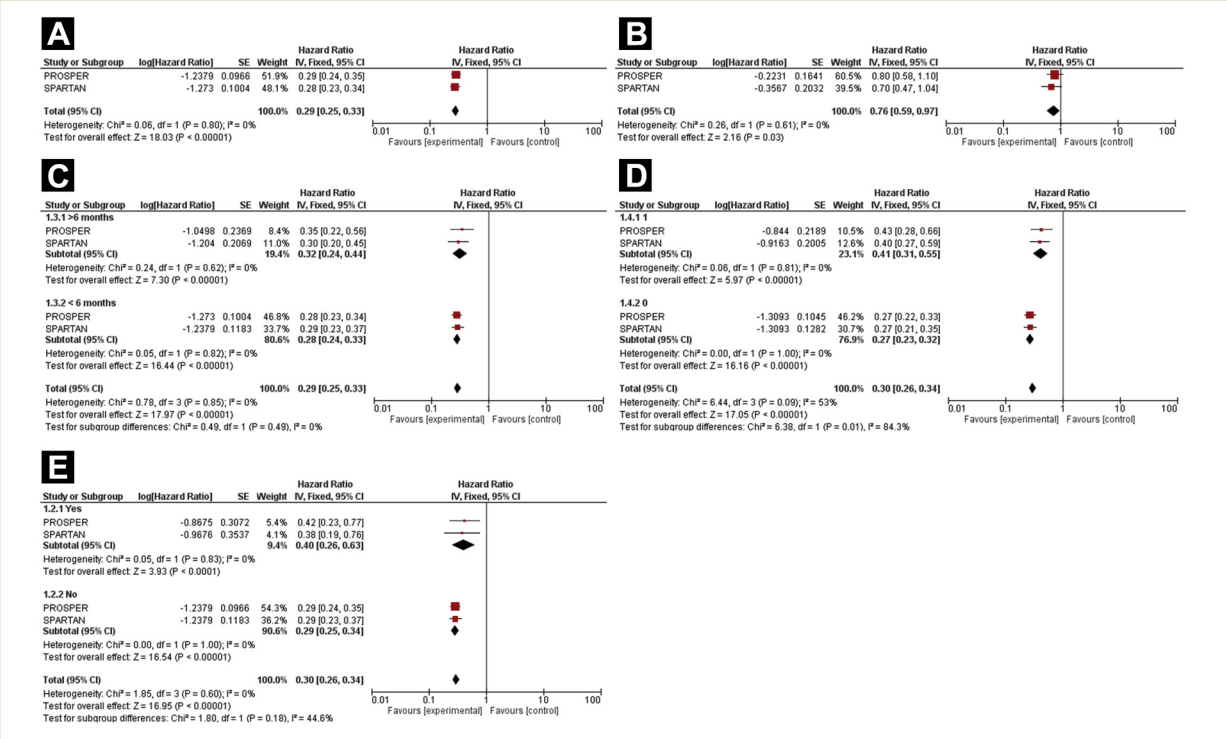
Figure 1 **Pooled Analysis for Time to Develop Metastasis and Overall Survival (A, B), Subgroup Analysis for Time to Develop Metastasis According to PSA Doubling Time (C), ECOG PS (D), and Concomitant Use of Bone-Targeted Agents (E)**



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

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