EUROPEAN UROLOGY XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Joaquin Mateo, Karim Fizazi, Silke Gillessen, et al. Managing Nonmetastatic Castration-resistant Prostate Cancer. Eur Urol 2019;75:285–93

We read with great interest the article by Mateo et al. [1] on the management of nonmetastatic castration-resistant prostate cancer. The PROSPER (NCT02003924) [2] and the SPARTAN (NCT01946204) [3] trials showed that enzalutamide and apalutamide improve metastasis-free survival (MFS) among patients without evidence of metastasis on conventional radiological imaging (computed tomography and bone scans). Since February 2019, data from the ARAMIS trial (NCT02200614) have become available [4], with similar MFS outcomes for darolutamide as for enzalutamide and apalutamide. It should be noted that the safety profile of darolutamide is promising because of its low penetration across the blood-brain barrier and low binding affinity for γ-aminobutyric acid type A receptors, as shown in preclinical studies.

However, the safety of darolutamide seems to be better than its actual effectiveness. In the PROSPER trial of enzalutamide [2], there was a hazard ratio of 0.29 for metastasis or death among a series of patients with a prostate-specific antigen (PSA) doubling time of 3.8 mo. The ARAMIS trial [4], in which there was a hazard ratio of 0.41 ratio for metastasis or death, enrolled patients with a longer PSA doubling time (4.4 mo) [1]. Could this dissimilarity be regarded as the reason for the discrepancy, or would a few weeks make such a difference in an aggressive setting?

A 6-mo threshold for PSA doubling time has long been considered a landmark: a shorter PSA doubling time is associated with a trend towards greater detection of metastasis via prostate-specific membrane antigen–based positron emission tomography (83% vs 60% for PSA doubling time of $<$6 mo vs $>$6 mo) [5].

Since biological aggressiveness below the 6-mo threshold has rarely been investigated, what would we expect in the case of a shorter PSA doubling time? Despite the apparent similarity, the PROSPER trial enrolled patients with more aggressive disease, as evidenced by data for patients assigned to the placebo group. The time to PSA progression in the placebo arm was shorter in the PROSPER trial (3.8 mo) than in the ARAMIS trial (7.3 mo), suggesting a more pronounced impact of enzalutamide, even for patients at higher risk of progression.

Safety and easy handling should complement the effectiveness of new hormonal agents; this issue should be further addressed before formulating recommendations based on drug toxicity.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Mateo J, Fizazi K, Gillessen S, et al. Managing nonmetastatic castration-resistant prostate cancer. Eur Urol 2019;75:285–93.
[2] Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465–74.
[3] Rachner TD, Tsourdi E, Hofbauer LC. Apalutamide and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:2541–2.
[4] Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019;380:1235–46.
[5] Pereira Mestre R, Treglia G, Ferrari M, et al. Correlation between PSA kinetics and PSMA-PET in prostate cancer restaging: a meta-analysis. Eur J Clin Invest 2019;49:e13063.

Bernardo Rocco
Maria Chiara Sighinolfi*
Department of Urology, University of Modena and Reggio Emilia, Modena, Italy

*Corresponding author. Department of Urology, University of Modena and Reggio Emilia, via del Pozzo 71, Modena 41100, Italy. Tel. +39 059 237170; Fax: +39 059 4222368.
E-mail address: sighinolfic@yahoo.com (M.C. Sighinolfi).

May 17, 2019

https://doi.org/10.1016/j.eururo.2019.05.030