

Reus, 25th of November 2021

Dear Reviewers,

Thank you very much for reviewing our editorial entitled: “Nonmetastatic Castration-Resistant Prostate Cancer: Novel Agents to Treat a Lethal Disease”

We sincerely appreciate all valuable comments and suggestions, which helped to improve the quality of the article. Appropriate comment suggested by the Reviewer N°1, ....” earlier initiation of the ARI’s may result in aggressive molecular subtypes that were not detected in the three recent trials due to time constraints” has been discussed and introduced on Section 2.2 Should we assess molecular determinants in nmCRPC? of the manuscript.

Smith<sup>[10]</sup> et al evaluated the frequency of AR anomalies, including AR-V7 expression, AR mutations, and AR amplification, before and after treatment with apalutamide plus ADT and impact on the exploratory endpoint PFS2 and time on subsequent therapy in patients with nmCRPC who were enrolled in the phase 3 SPARTAN study. Frequency of total AR anomalies was higher in patients at end of treatment than at baseline for both the apalutamide and placebo groups (apalutamide vs placebo at baseline: 16% vs 13% and at end of treatment: 20% vs 30%). Most patients with AR anomalies in the apalutamide group achieved a PSA response at 12 weeks. Following the end of apalutamide or placebo treatment, individual AR anomalies did not have a substantial effect on PFS2.

We also corrected a typo on Section 2.5 “determining”. Also, there 2 references as Abstract: ASCO and ASCO GU Congress 2020, where there is not PMID and DOI.

We hope that our manuscript will be acceptable for publication in World Journal of Clinical Oncology.

Best regards,

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