Re: Christopher J.D. Wallis, Zachary Klaassen, Bimal Bhindi, et al. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis.

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We read with interest the recent systematic review and network meta-analysis by Wallis and colleagues [1]. We would like to draw attention to some concerns about the methodological approaches used in this paper.

First, the specific objective and trial inclusion criteria are unclear, and therefore it is not clear why some trials were included and others were not. If the focus is high-risk and metastatic hormone-sensitive prostate cancer, then a number of additional trials in high-risk locally advanced disease would be eligible [2]. If the primary interest is metastatic disease, then it would have been better to restrict the primary analysis to those men. Unpublished trials have not been taken into account, and by excluding conference abstracts, the most up-to-date survival results of the CHAARTED trial [3] are overlooked.

Second, there have been considerable advances in network meta-analysis methodology in recent years and a number of software packages are available to conduct these analyses. For their primary analysis, however, the authors relied on a simple "indirect comparison" (whereby two pairwise pooled log-hazard ratio estimates are subtracted from each other and their variances summed), which does not fully estimate model heterogeneity or inconsistency. The authors only carried out a "validation" analysis using a Bayesian network meta-analysis package for R.

Third, in this particular network, the inclusion of two distinct treatment comparisons from the STAMPEDE trial [4] poses some particular challenges, in that the different treatment comparisons share common control-arm patients. In a network meta-analysis, this commonality must be considered to obtain results that take this correlation into account. There is no evidence that this was considered by the authors, and in fact the common control arm patients have been double-counted.

Finally, in the network meta-analysis context, there are not yet robust or widely accepted methods for assessing treatment-subgroup interactions. We would therefore question the focus given to subgroup analyses and would certainly caution against the approach used here, namely the comparison of pooled treatment effects within subgroups defined by, for example, age and disease volume, without formal and appropriate tests for interaction. This can lead to considerable bias [5,6] that is likely to be further exacerbated when these effects are indirectly compared. More research is needed before subgroup analyses can be performed reliably in the context of network meta-analysis.

Other factors not considered include changing prognosis or treatment effects over time and the potential impact of treatments used following disease progression. Many of these issues can only be addressed via collection of individual participant data. With all of this in mind, we would urge readers to treat the results and interpretation of this meta- analysis with some caution.

Conflicts of interest: The authors have nothing to disclose.

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