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REPLY TO:

Clarification to provide further understanding of the conduct and design of TROPIC: A Phase 3 trial of cabazitaxel versus mitoxantrone in patients with metastatic castration-resistant prostate cancer

Dear Editors,
Thank you for bringing to our attention the letter from *Johann de Bono, Liji Shen* and *Oliver Sartor* concerning our article entitled "*Efficacy and safety of second-line agents for treatment of metastatic castration-resistant prostate cancer progressing after docetaxel. A systematic review and meta-analysis*" published in the *Archivio Italiano di Urologia e Andrologia*. We wish to thank *Johann de Bono, Liji Shen* and *Oliver Sartor* for their interest in our work and we are grateful to the Editors for giving us the opportunity to respond to their comments and remarks.

Perletti and co-authors' response (Row 1): According to Cochrane standards, risk of bias is "*unclear*" when the available information is insufficient to allow evaluation of the risk. The fact that dynamic allocation was instigated in few occasions in the TROPIC trial makes the risk of selection bias difficult to evaluate. In this respect, a tradeoff between balance and predictability is a constitutive component of dynamic allocation strategies.

Perletti and co-authors' response (Row 2): When the study protocol is not available together with the study article (protocols were provided as online supplementary material of the AFFIRM and COU-AA-301 reports), or elsewhere in the internet, the evaluation of the risk of bias becomes more difficult and the level of uncertainty naturally increases. The risk of misinterpretation also increases when a journal sets a strict word count limit for the text of a trial report of considerable importance, and important information is presented in a very synthetic form.

Perletti and co-authors' response (Row 3): Although quality of life data were not collected, pain was an important component of the composite PFS endpoint of TROPIC. Pain is the typical endpoint that may be substantially biased when patients are unblinded to their treatment allocation.

Perletti and co-authors' response (Row 5): Unclear risk of bias does not represent a negative evaluation of the quality of the evidence. Simply, the assessors are waiving any evaluation of the risk of bias when full assessment is hampered by lack of information, ambiguity, or any other factor making it difficult to assign the score "*low*" or "*high*" to a specific item in the ROB tool. According to the opinion of the ROB evaluators, "*the last date a patient is known to be alive*" was not a detailed, unambiguous description of a censoring criterion. If death (with death mostly occurring a certain time after tumor, pain, or PSA progression) were considered as progression time point, the risk of bias would have been rated as high. Again, detailed information featured in an "*open access*" study protocol minimizes the margins of uncertainty in the evaluation of a manuscript.

Perletti and co-authors' response (Row 7): As specified above, an unclear risk of bias is not a negative evaluation of the quality of the evidence. The 25%/25% baseline prevalence of visceral disease is shown in Table 1. The *Bahl et al. 2013* paper (*Ann Oncol. 2013 Sep; 24(9):2402-8*) reports that for the updated > 2Y OS analysis baseline visceral disease was present in 15% and 19.4% patients in the cabazitaxel and mitoxantrone arms, respectively. The figures are too small to allow evaluation of the reasons for such (likely accidental) out-selection of patients with baseline visceral disease in the Cabazitaxel arm.

Perletti and co-authors' response (Remark 1): We regret this omission. Indeed, the time-to tumor progression is aligned with the rPFS definition, and the hazard ratio and confidence interval for this endpoint (0.61; 95% CI:0.49 to 0.76; P < 0.0001) could have been added to the plot in Figure 3. No further assessment was however possible, as pooled analysis of rPFS was only performed for studies including anti-androgen agents versus placebo.

Perletti and co-authors' response (Remark 2, Item 1): A comparison was not made nor attempted in that sentence, which was simply summarizing, at the beginning of the discussion section, the available evidence in terms of overall survival. To make clear that comparisons between such absolute differences are not feasible, we stated at the very beginning of the discussion: "*Different baseline characteristics between studies (e.g., the prevalence of highly-prognostic visceral metastases or severe pain at enrollment) likely explain the inter-study variability of overall survival, especially as assessed in the control arms of each trial*".

Perletti and co-authors' response (Remark 2, Item 2): That sentence had survival as subject. Mitoxantrone has indeed antitumor activity, but no effect on survival. In the introduction section of their report, De Bono and co-authors state that though mitoxantrone could be administered for its effects on the quality of life, at the time (year 2010) no intervention showed to increase survival in the post-docetaxel setting (*De Bono et al., Lancet 2010; 376:1147-52)*.

No conflict of interest declared.

References

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2. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol. 2013; 24:2402-8.

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