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LETTER TO THE EDITOR

First-line Therapy for Metastatic Castration-sensitive Prostate Cancer

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To the Editor: In this network meta-analysis, Zheng et al[1] concluded that when combined with androgen deprivation therapy, enzalutamide (Enza) is superior in prolonging progression-free survival (PFS), but is inferior to abiraterone acetate plus prednisolone (AAP) in terms of overall survival (OS), which is counter-intuitive. We believe Enza may give better OS than stated by the authors.

First, one key difference between this and other meta-analyses is the inclusion of data from the ARCHES[2] trial. When data from ARCHES are included in a meta-analysis by Wang et el,[3] Enza is shown to be the least effective treatment in terms of OS. In contrast, data from ARCHES were excluded from a meta-analysis by Sathianathen et al,[4] which showed the OS benefit of Enza was comparable to other treatments including androgen deprivation therapy and had the lowest absolute hazard ratio of 0.53. Although OS data were not mature at the time the data were first published, a more recent update on ARCHES after a median follow-up of 44.6 months also shows a hazard ratio of 0.66 (95% confidence interval = 0.53-0.81) for OS.[5] Inclusion of these data may allow a more comprehensive analysis, and highlight whether Enza has comparable or better OS than androgen deprivation therapy given its impressive PFS. Even if Enza has superior PFS but inferior OS, the authors propose that this discrepancy might be due to treatment sequence, as use of second-line Enza followed by AAP is more effective than vice versa. However, among the included trials, only 10% (57/597) of the patients in the LATITUDE trial and 2.6% (25/960) of those in the STAMPEDE trial received Enza after progression on AAP. In contrast, 27.5% (46/167) of the patients in the ENZAMET trial received AAP after progression on Enza; data on post-study therapies are not available yet for ARCHES.[2] Given this figure, we believe it is unlikely that the OS benefit for AAP is driven by the use of second-line Enza.

Second, in the exploratory analysis, Zheng et al[1] tried to compare the OS of different agents (AAP, Enza, apalutamide) with docetaxel and demonstrated superiority of AAP over docetaxel. However, several studies that the authors included in their analysis included patients with previous exposure to docetaxel, including the ARCHES (17.9% and 17.7% of patients in the treatment and placebo arms, respectively), ENZAMET (17% and 15%, respectively) and TITAN (11% and 10.4%, respectively) studies.[1] Early exposure to docetaxel may lead to acquired resistance upon recruitment, which adversely affects the OS data because of limited treatment options upon progression. These patients were explicitly excluded by Sathianathen et al.[4] In contrast, STAMPEDE trial recruited a broader population, including those with non-metastatic prostate cancer with high risk-factors. Such patients were excluded by Wang et al.[3] Whether these two groups

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of patients were excluded is not explicitly mentioned by Zheng et al.[1] Because underlying different disease stages and previous exposure of chemotherapy may be confounding, such data should be interpreted with caution.

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