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Letter to the Editor

Reply to Jeffrey Graham, Omar Abdel-Rahman, Toni K. Choueiri, and Daniel Y.C. Heng's Letter to the Editor re: Fabio Conforti, Laura Pala, Vincenzo Bagnardi, et al. Cancer Immunotherapy Efficacy and Patients' Sex: A Systematic Review and Meta-analysis. *Lancet Oncol* 2018;19:737–46

Outcomes of Metastatic Renal Cell Carcinoma by Gender: Contrasting Results from the International mRCC Database Consortium

Graham et al. [1] performed an analysis on patients with metastatic renal cell carcinoma treated with nivolumab or everolimus, and recorded in the International Metastatic Renal Cell Carcinoma Database Consortium. In this analysis, they assessed for sex-based heterogeneity of the efficacy of nivolumab. Their analysis was of great interest since it was based on individual patient data, including details on other relevant known prognostic factors, albeit the sample size was very limited: in particular, only 68 women received nivolumab, and presumably, the number of events observed was very small (unfortunately, no details on the number of events were reported).

Presented data show that nivolumab improved overall survival for patients of both sexes. The magnitude of efficacy of nivolumab was double for males than for females: men treated with nivolumab experienced 11.2 mo of median overall survival (OS) improvement as compared with men treated with everolimus, versus 5.8 mo of improvement observed in women. Assuming that the proportional constant hazards assumption holds, these median survival rates translate to OS hazard ratios of 0.54 in men and 0.72 in women.

Such larger amount of benefit experienced by men is entirely consistent with the results reported in our meta-analysis, which dealt with several malignant diseases [2].

Given the absence of statistical significance of the interaction test in their modestly sized series of nivolumab recipients, Graham et al. [1] concluded that patients' sex and magnitude of nivolumab efficacy are unrelated. We disagree with this conclusion, since insufficient statistical power of the interaction test, performed in such a small sample, does not rule out a clinically relevant difference

among male and females. Immunotherapy is effective for both males and females, but the magnitude of the effect is larger for males.

To note, none of the 20 randomized controlled trials (RCTs) included in our meta-analysis reported a statistically significant interaction between gender and treatment effect due to the limited statistical power of subgroup analyses (p values ranged from 0.08 to 0.95; these results are not reported in the original paper, but can easily be derived from the presented results).

Graham et al. [1] also pointed out that the hazard ratios of immunotherapy versus controls reported in RCTs for males and females were unadjusted for other possible confounders. However, our results are based on the data from randomized comparisons from RCTs, rather than on a consortium database of cases.

The issue of confounding in subgroup analyses from RCTs is subtle. As reported by VanderWeele and Knol [3]: “the effect of treatment within subgroups will not be confounded because treatment is randomized; but the effect of the secondary factor defining subgroups might be confounded since it is not randomized.” This means that we can safely say that the effect of immune checkpoint inhibitors is different between males and females.

On the contrary, we cannot conclude that the observed difference is due to a causal effect of sex per se. For this reason, we have extensively discussed in our paper potential biological and physiological differences between men and women, which may explain the causal relationship of observed heterogeneity.

We completely agree on the need for future prospective studies in this area, and hope that trials with adequate sample size and statistical power will be used to assess efficacy of anticancer immunotherapy for each gender in every disease- and treatment-specific context.

Conflicts of interest: The authors have nothing to disclose.

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