Clinical and Translational Oncology
https://doi.org/10.1007/s12094-020-02352-4

CORRESPONDENCE

Immunotherapy-based combinations versus standard first-line and hypothyroidism risk

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Received: 23 March 2020 / Accepted: 1 April 2020

Dear Editor,

We congratulate Buti et al. [1] for their beautiful meta-analysis on all available clinical data from randomized clinical trials evaluating the impact of immune checkpoint inhibitors (CKI) on the outcomes of patients with metastatic renal cell carcinoma (mRCC) in first-line setting. In their work, the authors showed that immunotherapy-based combinations were able to decrease the risk of death over the standard of care by 26% (HR 0.74; 95% confidence interval (CI) 0.60–0.92; $p = 0.006$), to decrease the risk of progression by 21% (HR 0.79; 95% CI 0.72–0.86; $p < 0.00001$), and to increase the relative risk of response by 40% (HR 1.40; 95% CI 1.11–1.77; $p = 0.006$). The authors did not report data on adverse events that are a relevant topic when a new treatment option arises. In particular, several studies showed that sunitinib is associated with a significant risk of developing all- and high-grade hypothyroidism [2], while endocrine dysfunctions among patients receiving CKI regimens were well described [3]. On the basis of these findings, which show a possible risk of hypothyroidism for both sunitinib and CKI, it could seem reasonable to extend the analyses performed by Buti et al. for the evaluation of the risk of hypothyroidism in patients who received immunotherapy-based combinations versus sunitinib.

The pooled analysis with a random-effects model revealed that the incidence of any grade hypothyroidism among subjects with CKI combinations was quite similar compared to subjects with sunitinib (risk rate (RR) = 1.03, 95% CI 0.72–1.46; $p = 0.88$; $I^2 = 88\%$; Fig. 1). The pooled analysis with a fixed-effects model revealed that the incidence of grade ≥ 3 hypothyroidism was higher without a statistically significance in patients treated with sunitinib than CKI combinations (RR = 1.14, 95% CI 0.41–3.13; $p = 0.81$; $I^2 = 0$; Fig. 2). In conclusion, nonetheless, our analysis presents limitations, such as different experimental arm combinations; literature review rather than a meta-analysis based on individual patients' data and, therefore, definitive conclusions need to be considered carefully; our data confirmed no increasing incidence in the RR for any grade and grade ≥ 3 hypothyroidism with CKI combinations for mRCC.

This comment refers to the article available online at https://doi.org/10.1007/s12094-020-02292-z.

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Published online: 20 April 2020

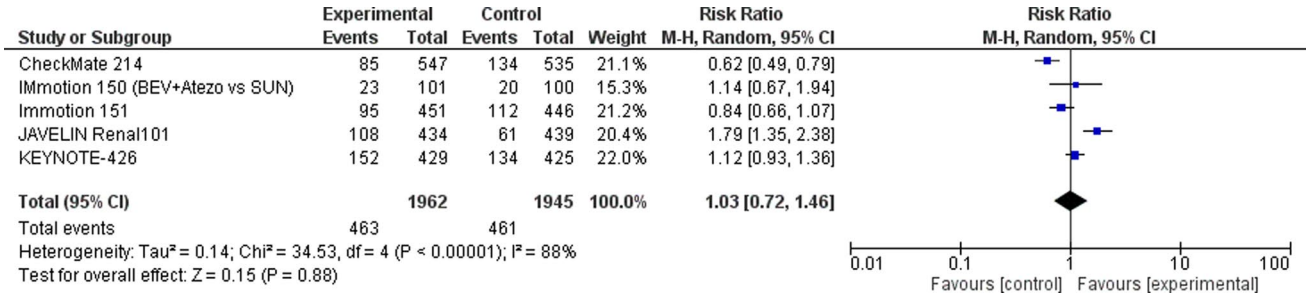

Fig. 1 Forest plots of risk rate (RR) for any grade hypothyroidism comparing experimental to sunitinib. The Chi-squared test showed high heterogeneity between the trials. The random-effects model was used

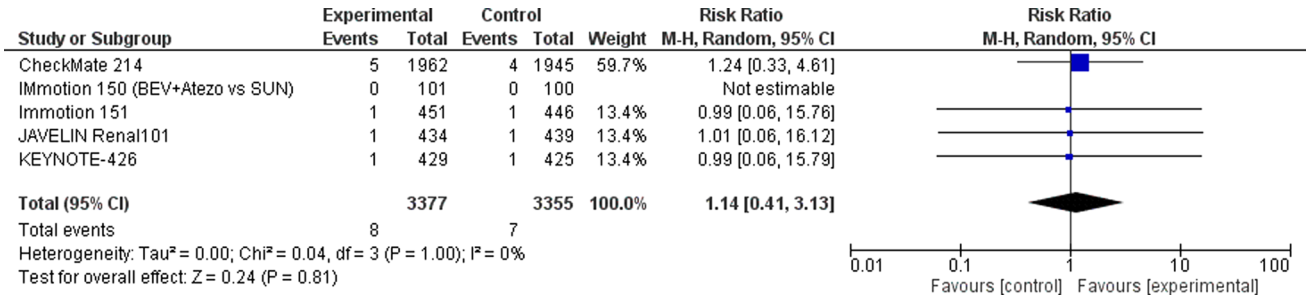

Fig. 2 Forest plots of risk rate (RR) for grade ≥ 3 hypothyroidism comparing experimental to sunitinib. The Chi-squared test showed low heterogeneity between the trials. The fixed effects model was used

Funding No funding.

Compliance with ethical standards

Conflict of interest The other authors declare that there are no conflicts of interest with this work.

Ethical approval This article does not contain any studies with human participant or animals performed by the author.

Informed consent For this type of study formal consent is not required.

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