Reply to Rizzo et al.

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Dear Editor,

We thank Rizzo et al. for their comments regarding our systematic review and network meta-analysis (NMA) comparing systemic treatments for unresectable hepatocellular carcinoma [1].

We appreciate the comments made about risk of bias. However, we considered these limitations in our study and, after careful evaluation, still assessed the risk of bias as generally low as 7 of 9 studies had a low risk of bias for at least 4 of 7 domains. Considerations of heterogeneity are important and were assessed in the Source Data Analysis subsection and online supplementary Table 3 in our article. Random-effects models incorporated measures of heterogeneity in the analyses. In our network, between-trial heterogeneity could not be assessed solely on the basis of the data in the network because of the very limited number of trials per pairwise comparison (a maximum of 7 trials with data could be considered, and there was a maximum of 2 trials comparing the same treatments) [2]; the Bayesian analyses borrowed information from previously published studies [3].

We agree with Rizzo et al. that adverse events and safety profiles are more difficult to compare using standard Bayesian NMA methods due to the reasons mentioned in the Discussion section.

Rizzo et al. suggest that Bayesian NMA may be linked with inflation of type I and II errors. However, inflation of type I error applies only in repeated testing without

considering a spending in the context of a living NMA with continuous updating [4]. This is not the case for our study [1]. Furthermore, the results of each meta-analysis indicate the current best evidence and need to stand on their own merit, as recommended by the Cochrane Expert Panel [5]. Finally, because NMAs generally analyze clinical trial data, statistical power to detect treatment differences can potentially be increased. In our case, uncertainty was relatively large due to the limited number of trials informing each pairwise comparison.

While we do believe that NMAs can be very informative to indirectly compare treatments based on available clinical trials, we also believe that clinical trials should remain the gold standard to evaluate new potential standards of care whenever clinically feasible.

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Statement of Ethics

The authors have no ethical conflicts to disclose for this systematic literature review and meta-analysis.

Conflict of Interest Statement

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Author Contributions

All authors participated in the writing and editing of the report and accept responsibility to submit for publication.

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