Peer Review File

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Review Comments

Reviewer A

The paper by van Gool and colleagues presents a careful and well-researched assessment of the recent publication by Liau et al., that recently appeared in JAMA Oncology. The authors are experts in the field, and their opinion must be taken seriously, and this paper is certainly worthy of publication, with a few necessary modifications, as follows:

Comment 1: The following sentence needs to be clarified, as it is unclear what is meant here (line 70): "At least the Hazard ratio, in comparison to an ECA of relapsed patients, was stronger when DCVax®-L was used without TMZm at time of relapse."

Reply 1: We thank the reviewer for pointing the need of clarification. We adapted the text.

Changes in the text: Line 72-75: At least the Hazard ratio, here reflecting the relative risk for mortality in comparison to the ECA, was stronger reduced (0.58) in the patients with recurrent GBM receiving DCVax®-L, as compared to the Hazard risk reduction (0.8) upon DCVax®-L treatment in the newly diagnosed patients under chemotherapy, suggesting that DCVax®-L might be more effective in patients outside chemotherapy.

Comment 2: Lines 93 – 97: it should be included here that Liau et al. specifically conducted a sensitivity analysis precisely to address the point raised by the authors. This information is found in the Supplement to the Liau et al. publication, as follows: "In the sixth sensitivity analysis, dropping 2 of the 5 comparator studies because it was not clear whether they had excluded patients with early progression, the HR remained the same (0.80 in both)." This demonstrates that Liau et al. recognized the potential of early progression to influence the outcome, and addressed it appropriately, and that the results showed that at least in this study there was no effect from this potentially confounding factor.

Reply 2: We agree with this comment, and adapted the text.

Changes in the text: Line 99-108: Nevertheless, the authors specifically conducted a

sensitivity analysis precisely to address this critical point (1). In the sixth sensitivity analysis, published in the Supplements, two of the five comparator studies were dropped because it was not clear whether they had excluded patients with early progression, and the HR remained the same (0.8). This demonstrates that the authors recognized the potential of early progression to influence the OS, and addressed it appropriately. The results showed that at least in this study there was no effect from this potentially confounding factor, making the improvement of OS due to DCVax®-L reliable. Moreover, the significant OS data and strong hazard ratio observed in the relapsed patients and their matched ECA might have the strongest value and might be most meaningful to demonstrate efficacy of DCVax®-L.

Reviewer B

Comment 3: The DC vaccination is an important topic of discussion in the neuro-oncology field. Therefore, a phase III study can be a breakthrough. Your article discusses this topic, but I would suggest presenting it as a systematic review with specific paragraphs, such as background/introduction, scope of the article, methods, results, discussion, and limitations. It is not clear what is the nature of the article, and it seems more likely of a chapter in a book rather an article.

REPLY

Reply 3: We were asked to write an EDITORIAL COMMENTARY, and kept to the foreseen instructions to authors. We therefore cannot follow the suggestion.