Reviewer's report

Title: MRP3: A molecular target for human high-grade glioma immunotherapy

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Reviewer: Steven De Vleeschouwer

Reviewer's report:

1. Is the question posed by the authors well defined? 
   Yes
2. Are the methods appropriate and well described? 
   Yes
3. Are the data sound? 
   Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? 
   Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? 
   Yes
6. Are limitations of the work clearly stated? 
   No
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? 
   Yes
8. Do the title and abstract accurately convey what has been found? 
   Yes
9. Is the writing acceptable? 
   Yes

The authors are to be gratulated for the interesting research they performed. This work reflects a very relevant field of research for innovative anti-glioma therapies. The methodology is sound and the possible future applications promising. Some smaller critical reflections, however, can be made.

- Major Compulsory Revisions

1. At several occasions throughout the manuscript there is a confounding use of and referral to either an absolute absence of expression of MRP3 in normal tissues and a relative overexpression of MRP3 in glioma tissues. The fact that '3
and 10-fold expression’ is used, only justifies the use of a relative notion of expression. In e.g. the second paragraph of the discussion (first sentence) or e.g. the last sentence of the first paragraph on p.16), the notion of ‘no expression of MRP3 in normal tissue’ is erroneously being used in a rather absolute term, internally conflicting with the notion of ratio’s to support the overexpression of MRP3 in glioma tissue. In the manuscript, the authors should consistently use the more relative notions of expression.

2. First paragraph of the discussion: talking about IDEAL antigens for immunotherapy, the authors should rephrase the prerequisites. As it is written in the current manuscript, it seems as if a ‘weakened version’ of the ideal characteristics is being used to maximally fit with the data of MRP3. The ideal antigen should a) be expressed uniformly and exclusively in tumor tissue, b) not (at all) in normal tissue, c) indeed being expressed in an accessible fashion in the tumor cell or environment at a sufficiently high density and d) being crucial for tumor (cell) survival. By rephrasing it this way, it becomes clear that MRP3 is indeed promising, but not yet the magical bullet.

3. P.22, last sentence. The optimal route for administration of mAb’s to tumor in the CNS is mentioned to be the local delivery in (or around) the resection cavity, eventually using convection enhanced delivery. A rather old reference (48) is being used to support this notion, but it should be made clear to the readership that especially these focal deliveries have important limitations: passive microdiffusion only happens to a very poor amount given the gliosis reaction in the wall of the surgical cavity and convection enhanced delivery should take into account modern calculations ofr isodose delivery distributions to really cover the relevant areas.

- Minor Essential Revisions

1. On page 19, second paragraph under ‘Immunohistochemical analysis’, reference to figure 4 is used three times instead of figure 3: this should be corrected.

- Discretionary Revisions

1. It is not clear why the authors use the age cut-off value of 45 years in the survival analysis: median age in this patient population is between 55 and 60 making ‘45 years’ a bit arbitrary as a cut-off value. If they built on specific publications, it might be good to acknowledge them.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests,