Reviewer's report

Title: DCE-MRI assessment of the effect of Epstein-Barr Virus-encoded latent membrane protein-1 targeted DNAzyme on tumor vasculature in patients with nasopharyngeal carcinomas

Version: 3 Date: 29 August 2014

Reviewer: James P O'Connor

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Major Compulsory Revisions

1. Ktrans is measured in a hot spot region only. This is non-standard (see O'Connor 2012 Nat Rev Clin Oncol - ref 15 in the ref list) and is a weakness. Please justify why a whole tumour ROI has not been performed.

2. The quality of the figures and tables are poor, but that can be rectified.

3. Lines 158-160 state that this is the first study of an LMP1-targeted DNAzyme using DCE-MR, but the first line of the results section states 'it was previously observed that Ktrans values undergo a rapid decline following the administration of LMP1-targeted DNAzyme …'. These two statements seem to contradict each other. Please clarify.

4. The two small groups will not necessarily have comparable baseline characteristics. Therefore, I think all tests between the 2 groups are misleading and I would remove entirely. They simply muddy the data. Instead, I suggest the authors focus on how group 1 changes …. then group 2.

5. Too many p values are cited on page 10 – a table would be better. This should include all the DCE parameters and volume. It is illogical that tables 2 and 3 describe this for kep and ve but not for Ktrans. Please re-order this information to include Ktrans. If necessary this can be split into several tables.

6. There appears to be an issue with multiple comparisons, as the analysis has two groups each of which has 4 time points and 3 parameters, one of which is the ratio of the other two. How can a p value of p=0.05 be justified as indicating significance?

Minor Essential revisions

1. The abstract needs reworking taking in my criticisms about the way the results are presented (see below).

2. Line 152 should be changed from ‘blood flow’ to ‘blood flow and permeability’

3. The terminology does not quite follow generally accepted guidelines from Tofts 1999 JMRI – the Ve term should have a small and italic v; the trans of Ktrans should be italic.

4. State the precise contrast agent used, dose and manufacturer in ‘Methods’
5. State the manufacturer of the power injector in ‘Methods’

6. Why are ‘qualitative’ maps referred to on line 233 as this plays no part in the data results?

7. Line 286 refers to Ktrans values and then cites them as being in Table 2, but the Table 2 legend on p24 refers only to kep – this does not make sense and needs rectifying.

8. The discussion is generally too long. The first paragraph in the discussion is irrelevant and needs to be removed. The beginning to paragraph 2 can be shortened (benign v malignant section is also irrelevant).

9. The results do not need to be repeated in detail in the discussion (e.g. lines 364-365).

10. The first 2 sentences in the conclusion are general points and can be removed.

11. Figure 1 needs reworking. It is more conventional to plot the data from each group as a line (with 4 points) and place CI on this, rather than using box plots straight out of the statistical package. The quality of the figure also needs improving. The y axis needs a label. Any statistical differences between the 2 groups at any time point require clear marking on the figure. This will make the message much clearer – that Ktrans reduces throughout the experiment with the combination therapy but only at the last time point with XRT. This message is not clear at the moment.

12. Figures 3 and 4 add little. Please derive a more focussed figure that demonstrates Ktrans changes in each group using sample images (ideally as just one figure).

Discretionary Revisions

1. Figure 2 can be relegated to supplementary material.

2. Few studies have done DCE-MR in such detail with XRT alone so this is interesting in its own right – this point can be made more forcefully in the discussion.

3. The relationship between DCE-MR and VEGF has only been explored in a few studies and is still not well understood. This point should be made in the discussion after line 372 and can cite Mitchell 2010 Annals Oncology 21:1982-9 or other suitable reference.

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests