Reviewer's report

Title: Concerns about anti-angiogenic treatment in GBM patients

Version: 2 Date: 9 April 2009

Reviewer: Jeremy Rich

Reviewer's report:

Although I find several valuable points in this manuscript, I do not believe that this manuscript currently warrants publication without revision. The authors’ response to prior critiques was incomplete and additional primary publications have been recently published rendering this manuscript out of date. On one hand, I agree with the authors that there are concerns that must be addressed with bevacizumab treatment, but they must use their appropriate rigorous criteria when presenting their own data. I find the interpretations occasionally biased. I would advocate the presentation the published data objectively initially then inclusion of the authors’ own data and finally interpretation clearly stated as such.

The authors continue to combine some aspects of a position piece, review, and data presentation without full development. The authors should present their arguments as opinion, unbiased review, or reporting of data. I would suggest that the authors go well beyond their preliminary revisions.

Major Compulsory Revisions:

1. There are important new studies that must be included (some support the authors concerns and add objective data):


   e. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Pàez-Ribes M, Allen E, Hudock J, Takeda


2. The authors should include all of the published glioma studies on bevacizumab (not a selected few) and report the direct results before any opinion. I disagree that only the glioblastoma studies should be presented. Of note, high grade gliomas include both grades III and IV. The studies with specialized imaging are also informative and bear inclusion.

3. The authors should not present patient data in the absence of information about the patient and full treatment. It is frequently the case that patients have distant tumor cells even at the time of diagnosis so presenting only isolated cases of bevacizumab treated patients without controls is exactly the deficiency that the authors criticize about the larger published clinical trials. I was hoping that the criticisms that were raised (lack of randomization, use of PFS vs. OS) that are very valid would be addressed in their own data.

4. The authors should particularly strive to be objective and data centric in the abstract and avoid opinion.

5. AZD2171 is not the same as bevacizumab and these data should be presented in clear separation. For unclear reasons, the VEGF receptor antagonists are not identical to the effects of either bevacizumab or VEGF-trap.

6. The authors should remove the statements that are not objective except when clearly presenting opinion. For example:

a. Whilst clinical symptoms are tempered by anti-angiogenic treatment, the disease continues to furtively invade

b. Although angiogenesis inhibition is of considerable value for symptom reduction in GBM patients, the possible lack of a true anti-tumour effect

c. this tumour also furtively invades

d. Data on overall survival prolongation are less convincing and even conflicting between studies.

e. Few clinicians doubt

f. …and seems to be even more active

g. Available data on survival prolongation are less robust and even conflicting.

Minor Essential Revisions:

7. Of minor note, the “BBB” designation has been replaced by the “neuro-vascular unit”.
Despite these concerns, I believe that this manuscript (if revised) adds thoughtfully to the literature.

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

**Quality of written English:** Needs some language corrections before being published

**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.