Author's response to reviews

Title: Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme

Authors:

Joost J Verhoeff (j.j.verhoeff@amc.uva.nl)
Olaf van Tellingen (o.v.tellingen@nki.nl)
An Claes (A.Claes@pathol.umcn.nl)
Lukas J Stalpers (L.Stalpers@amc.uva.nl)
Myra E van Linde (M.E.vanLinde@amc.uva.nl)
Dick J Richel (D.J.Richel@amc.uva.nl)
William PJ Leenders (W.Leenders@pathol.umcn.nl)
Wouter R van Furth (w.r.vanfurth@amc.uva.nl)

Version: 3 Date: 26 May 2009

Author's response to reviews: see over
To the Editor in Chief of BMC Cancer
BioMed Central
Middlesex House
32-42 Cleveland Street
London W1T 4LB, UK

REFERENCE: MS: 2824640032364656

Amsterdam, 25 may 2009

Dear Editor,

We would again like to thank you for the opportunity to further improve our manuscript previously entitled “Concerns about anti-angiogenic treatment in GBM patients” which we submitted for possible publication in BMC Cancer, as Debate article.

According to your advice we have changed the title to:
“Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme”

Attached please find a detailed response to each of the reviewers’ comments and suggestions. The re-revised version of the manuscript is attached with changes marked with yellow.

A Debate article is not only complex to write, it is also difficult for reviewers. Particularly, reviewer Jeremy Rich has some very valid points, but in addition he would like us to present a complete review of the literature. We tried as much as possible to accommodate his concerns. However, the nature of a Debate article is such that selection of relevant data needs to be made. That does not mean that not all sides of the arguments have been taken into consideration; it means that in presenting our case we made a selection. References are complete now and up to date.

We believe that our contribution is still timely; currently the debate on this topic is ongoing. This is in part a response to the fact that bevacizumab received FDA approval for treatment of recurrent GBM only a month ago. Delay in publication was hopefully not too long.

Yours sincerely,
On behalf of all authors,

Wouter R. van Furth, MD PhD
Department of Neurosurgery
Academic Medical Center, University of Amsterdam
P.O.Box 22660
1100 DD Amsterdam
The Netherlands
tel. +31-20-5669111
fax. +31-20-6091278
e-mail: w.r.vanfurth@amc.uva.nl
**REFERENCE: MS: 2824640032364656**

**Original Title:** Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?

**NEW TITLE:** Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme

**Reviewer:** Eric Wong

**Reviewer's report and authors' responses:**

1. None.
   
   a. We thank Dr. Wong for his comments on the previous version of the debate article; this response underscored the value of the manuscript in the present ongoing discussion in the community. The recent FDA approval is now also included into the manuscript (please see page 4, lines 6 to 9).
REFERENCE: MS: 2824640032364656

Original Title: Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?

NEW TITLE: Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme

Reviewer: Andrew D. Norden

Reviewer’s report and authors’ responses:

1. The authors have addressed all of the salient issues mentioned in the initial reviews.

2. They may wish to include these important reports that were published since the manuscript was initially submitted: Cancer Cell. 2009 Mar 3;15(3):220-31 & Cancer Cell. 2009 Mar 3;15(3):232-9.
   a. We now incorporated these important articles, they do further emphasize the message of our debate article (please see page 9, lines 1 to 3).

3. There is a typographical error in line 1 ("mamma").
   a. We replaced “mamma carcinoma” by “breast cancer” (please see page 4, line 1).
REFERENCE: MS: 2824640032364656

Original Title: Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?

NEW TITLE: Concerns about anti-angiogenic treatment in patients with glioblastoma multiforme

Reviewer: Jeremy Rich

Reviewer’s report and authors’ responses:

1. 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.

   a. Thank you for your valuable comments. As in the previous revision, we have thoroughly revised our manuscript and taken into consideration all of your critics. We hope that we have been complete this time. A Debate article is complex to write. We tried to clearly separate fact from opinion. We are motivated to write this paper by our own experiences in treating these patients. However, for clarity sake we will not present our own survival data here. We did review all published data and references are clearly indicated. Our opinion is based on these data and as such presented in the paper. Recent published data does support our concerns and we believe that a Debate article is still timely and of interest for a larger group of physicians.

2. There are important new studies that must be included (some support the authors concerns and add objective data):
• Silencing or fueling metastasis with VEGF inhibitors: angiogenesis revisited. Loges S et al
• PDGF-C mediates the angiogenic and tumorigenic properties of fibroblasts associated with

a. Thank you for listing these key publications that were published after submitting
the revision. Now we included these important studies in our re-revised
manuscript, but not:
• Nghiemphu PL, this is a retrospective comparison of a conventionally treated
• Crawford Y, discussing the expression of proangiogenic PDGF-C as a potential
therapeutic target is beyond the scope of this Debate article.

3. 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.

a. Although this debate paper is not meant to be a complete literature review, it
makes sense to be unbiased in considering all relevant data. We have done so
and tried to report a good balance of published literature. However, we can not
be complete, since it is a debate and not a review article. Therefore, grade III
tumours were not included.

4. 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.

a. We have refrained from presenting any new survival data of our own patients or
studies. We share the raised concerns and our own data are subject to that too.
The reviewers’ objection is quite right. Nevertheless, we use own patient
material only to illustrate a certain point known in literature, not as prove to
support our opinion.

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

a. We followed your advice and rewrote most of the abstract.

6. 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.
a. We clearly referenced the manuscripts of AZD2171 and bevacizumab, an obvious separation is therefore already made (please see page 5, lines 14 to 16).

7. The authors should remove the statements that are not objective except when clearly presenting opinion. For example:
   1. Whilst clinical symptoms are tempered by anti-angiogenic treatment, the disease continues to furtively invade.
   2. Although angiogenesis inhibition is of considerable value for symptom reduction in GBM patients, the possible lack of a true anti-tumour effect
   3. this tumour also furtively invades
   4. Data on overall survival prolongation are less convincing and even conflicting between studies.
   5. Few clinicians doubt
   6. ...and seems to be even more active
   7. Available data on survival prolongation are less robust and even conflicting.

a. We adapted these sentences, see highlights:
   1. Published data support that clinical symptoms are tempered by anti-angiogenic treatment, **but that tumour invasion continues**. (please see page 2, line 12)
   2. Although angiogenesis inhibition is of considerable value for symptom reduction in GBM patients, **lack of proof** of a true anti-tumour effect (please see page 2, line 22)
   3. this tumour also invades (please see page 3, line 11)
   4. Available data on survival prolongation are less **robust (phase II) and sometimes even conflicting**. (please see page 11, line 8)
   5. Few clinicians doubt -> removed. (please see page 5, line 5)
   6. ...and is even more active (please see page 5, line 9)
   7. **Due to a lack of large phase III studies, reliable data on overall survival prolongation are not available.** (please see page 4 line 6)

8. Of minor note, the “BBB” designation has been replaced by the “neuro-vascular unit”.

a. Although the term neurovascular unit has been proposed as an alternative to blood brain barrier in the literature, as it may provide a more comprehensive specification, the term blood brain barrier is still more widely used. In order to avoid confusion by non-specialist readers, we would favour the use of the blood brain barrier (BBB) throughout our manuscript.

9. Despite these concerns, I believe that this manuscript (if revised) adds thoughtfully to the literature.

a. I hope we were able to take away your major concerns.