

Author's response to reviews

Title: Hypothesis: Primary antiangiogenic method proposed to treat early stage breast cancer

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Author's response to reviews:

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Dear editors of BMC Cancer

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Hypothesis: Primary antiangiogenic method proposed to treat early stage breast cancer. Michael W Retsky, William J Hrushesky and Isaac D Gukas

This manuscript has been revised in accordance with the comments from the two reviewers Drs. Bachelot and Dabrosin. The comments are listed below together with the changes we made. For a few comments, we disagree with the reviewers and present our reasoning.

Bachelot review criticisms

1. not sufficiently supported by data to be rapidly tested in clinical trial

We agree and that is why we present this document as a hypothesis to stimulate discussion and stimulate efforts to support or deny the proposals laid forth.

2. Idea is not new

We disagree. Long term use of Endostatin is not new but to use it in early stage breast cancer starting before surgery is a new idea. See DS section, paragraph 7

3. Authors must give a broader view and interpretation of preclinical and clinical data.

We accept this viewpoint and have added discussion to paper as shown below.

4. dormant avascular micromets have not seen in human bc

We agree. We have reported strong indirect evidence but have no direct

evidence that dormant avascular exist in breast cancer nor that surgery can stimulate these to grow. This is noted in document. See Background Paragraphs 6 and 7.

5. Preclinical data are not straightforward and not discussed sufficiently in document. Mostly derived from the famous Lewis lung experiments. LL does not represent the full biology of metastases. Lewis lung is a poor predictor of drug action in humans according to Staquet Cancer treatment Reports 67:753, 1983.

We agree that preclinical data need more discussion. The document has additional discussion of preclinical data. See Background Paragraph 7.

We agree that our model is closely related to Lewis lung experiments of O'Reilly. This is now noted in the document. See Background Paragraph 7. We think Lewis lung behavior where the presence of the primary tumor keeps micrometastases avascular and dormant is one reasonable description of what happen in node -positive premenopausal breast cancer. Retsky and O'Reilly were in the Folkman lab in 1995-1998 and reviewed the breast cancer data together and came to the conclusion that there is strong similarity. We disagree that Lewis lung is a poor predictor of drug action in humans. From the Staquet 1983 paper Table 8, LL had a PV+ (predictive value of a positive screen) of 0.82 while the other models listed had 0.59 to 1.00 for all sites.

6. The idea that giving continuous SC Endostatin has been extensively tested with mixed results.

We agree and this is noted in the paper. However, as discussed in the paper, the idea that giving continuous Endostatin in early stage breast cancer starting before primary surgery has not been tried and there is good reason to suspect it will work. See DS section paragraphs 6 and 7.

7. Boehm et al data (Nature 1997) has not been reproduced. Reviewer's and other's studies show no in-vivo angiogenesis inhibition using a retrovirus encoding a soluble form of Endostatin.

This is now noted in the paper. See DS section Paragraph 6.

8. Our document states DS data show Endostatin is not associated with wound repair. This can be interpreted to mean that Endostatin has no antiangiogenic activity.

We agree with this possibility and it is now added to the paper. See DS section Paragraph 5.

9. Other hypotheses related to trisomy 21 can explain the lack of breast cancer in DS.

We agree and this is now added to the paper. See DS section Paragraph 4.

10. Sund et al (PNAS 2005) report that 1.6 fold increase in Endostatin in an animal model slowed but did not prevent cancer. Manuscript suggested this as one test of hypothesis.

We agree and have changed the proposed test to be conducted with a breast cancer model since there is a predisposition to dormancy rather than any model where there may be no predisposition to dormancy. See Conclusions section, Paragraph 4.

11. Endostatin has been tested in highly publicized and well conducted clinical trials with no anti-tumor activity or any biologic activity of Endostatin either in wound healing or tumor antiangiogenesis. In contrast, bevacizumab and sunitinib have shown benefit in clinical trials.

We added this to the document but stress that this was not conducted in early stage breast cancer nor started before surgery as we suggest. See DS section paragraphs 6 and 7.

12. There are no peer published data on Endostar. Suggests it is not reasonable to proposed use of that drug at this time.

We agree and have deemphasized Endostar noting these concerns. See DS section paragraph 8.

Dabrosin review criticisms

1. Hypothesis is based on computer simulations. Some animal models have shown tumor growth after surgical removal of primary tumor in some cancers. Authors provide no evidence that this happens in humans.

We agree but note that if we had data, we would not need to present this as a hypothesis. See Background paragraph 6

2. Long term use of antiangiogenics has not been evaluated and there might be serious side effects. For example it might induce castration in premenopausal patients. That itself might improve outcome. How will we know that any benefit is due to antiangiogenic treatment?

We agree and have added this to the document. However our paper is a hypothesis and not a proposal for a phase II clinical trial. See Hypothesis section, paragraph 5.

3. Hypothesis is interesting but is not novel and maybe now is the time for authors to perform the proposed trial.

We claim that the hypothesis is novel for reasons described above. Our desire is to publish this as a hypothesis to stimulate discussion and stimulate attempts to test the ideas in preclinical experiments that we describe. Afterwards if these arguments seem valid, clinical trial can be conducted at our institutions or at other institutions.

We thank the reviewers for tough but fair criticisms. We think the paper is improved as a result of addressing these comments.

Sincerely yours,

Michael Retsky

William Hrushesky

Isaac Gukas