Reviewer's report

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

**Version:** 2 **Date:** 13 October 2008

**Reviewer:** Charlotta Dabrosin

**Reviewer's report:**

The paper by Retsky et al the authors put forward a hypothesis of early angiogenesis inhibition, which would decrease risk of recurrence in cancer patients in general and breast cancer patients in particular.

**Major Compulsory Revisions**

The present hypothesis is based on previous review articles, previously published hypothesis, and studies based on computer simulations. No original research of human cancer performed by the group is the base for the present hypothesis. The statement that the growth rate of metastatic lesions increases after removal of the primary tumor has been shown in some animal models for some particular cancers. The authors have provided no evidence that this occurs in humans. This is key for the present hypothesis.

The use of angiogenesis inhibitors for a long period of time has yet not been evaluated and at this point it is not possible to state that this is not accompanied with serious side-effects. Angiogenesis inhibition may cause impaired ovulation and thereby induce castration in the pre-menopausal patient. This leads to very low circulating estrogen levels. This would most certainly have a huge impact on breast cancer as we know that in ER positive patients a reduction of the estrogen levels is a potent therapy against the disease. How would we know that the benefit is dependent on angiogenesis inhibition and not by the reduced estrogen levels? This has to be discussed in detail.

Although the hypothesis is interesting it is not novel and maybe now is the time for the authors to perform the clinical trial as they propose in the paper.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
No to all of the above.