Reviewer's report

Title: Phase II randomized study of neoadjuvant METformin plus letrozole vs placebo plus letrozole for estrogen receptor positive pOstmenopausal bReast cancer (METEOR)

Version: 3 Date: 11 October 2013

Reviewer: Ryan Dowling

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In the study protocol entitled “Phase II randomized study of neoadjuvant METformin plus letrozole vs placebo plus letrozole for estrogen receptor positive pOstmenopausal bReast cancer (METEOR)” Kim et al. describe a clinical trial designed to evaluate the benefit of combining metformin with the aromatase inhibitor letrozole. The authors plan on assessing clinical response rates in patients and hope to characterize the effects of metformin on tumour biology. The results of the study may help elucidate the mechanism of action of metformin and will provide useful information on whether patients receiving letrozole may benefit from metformin or other therapies designed to maintain insulin homeostasis or target AMPK signalling. However, the authors need to clarify a number of issues, which are listed below. In particular, the authors need to provide a more detailed description of the eligibility criteria and perform a more thorough analysis of the effects of metformin on cell signalling and tumour biology. In addition, they should consider including change in Ki67 staining as a primary study endpoint. Addressing these issues would strengthen the trial design and increase the overall value of the study.

Major Compulsory Revisions

1. There are a number of grammatical errors in the manuscript that need to be corrected.

2. The authors need to provide a more thorough description of the eligibility and exclusion criteria. For example, women with fasting glucose greater than 7mM should be excluded as they may have type 2 diabetes. In addition, patients with a history of lactic acidosis or high alcohol consumption should also be excluded to avoid increasing the potential for adverse effects of metformin.

3. The authors should consider assessing physiological markers (fasting glucose and insulin, Hb1Ac, c-peptide and IGF-1) at 4 weeks rather than 12 to correspond to the timing of tumour tissue collection. This will allow the authors to assess whether changes in patient physiology correlate to changes in tumour biology.

4. In addition to Ki67 and phospho-S6K, the authors should also assess AMPK phosphorylation (T172) in tumour tissue since AMPK is a target of metformin and
responsible for many of the potential anti-cancer effects of the drug. The expression of OCT1, one of the transporters responsible for cellular uptake of metformin, should also be examined in tumour tissue. Expression of the insulin receptor should also be assessed as a measure of potential sensitivity to the systemic, insulin-lowering effects of the drug. The authors should also consider measuring apoptosis in tumour material to fully characterize the potential anti-tumour effects of metformin.

5. In the discussion, the authors mention that “this is the first study evaluating direct anti-tumor effect of metformin in human breast cancer.” However, there have been numerous other trials focussing on the anti-cancer effects of metformin in breast cancer patients (please see Hadad et al., 2011, Niraula et al., 2012, and Bonanni et al., 2012).

Discretionary Revisions

1. The primary endpoint of the study is clinical response, as measured by calipers. The authors should consider using change in Ki67 staining as an additional primary endpoint. Ki67 is known to be responsive to short term interventions of metformin and other anti-cancer drugs and changes in Ki67 in the neoadjuvant setting often emulate long term effects of cancer therapies in adjuvant studies. Using Ki67 as an endpoint would be particularly informative in the event that metformin has little impact on tumour size and clinical response rates.

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: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.