Author's response to reviews

Title: E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumour cell migration and invasion

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Version: 2 Date: 29 June 2011

Author's response to reviews:

Dear Dr Gallick

Thank-you for considering our manuscript entitled ‘E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumor cell migration and invasion’ for publication in BMC Cancer. While we appreciate that the manuscript does not fully address the mechanism of action of E7080 we believe that it does contribute to our understanding of this exciting multi-kinase inhibitor that is showing promising efficacy in the clinic. In line with your own comments and those of the reviewer we have amended the text. All changes have been highlighted in the uploaded document and outlined below is the point-by-point description of the changes.

Major Revisions

1. We agree that the data presented does not provide insight into which patients would benefit from treatment with E7080. We did not mean to imply that in the text. However, we believe that understanding the direct tumor effects of multi-targeted agents is important and by showing that E7080 can inhibit invasion and migration may provide additional benefits.

2. The testing of potential anti-invasives in the clinic is difficult and as yet has not been adequately explored. Indeed as the reviewer points out, Src inhibitors (and also PDGFR inhibitors such as imatinib (point 3)), that are potent inhibitors of invasion have not yet been shown to have a role in the treatment of solid tumours. This most likely reflects deficiencies in clinical trial design and the identification of which patient sub-group would benefit from treatment with anti-invasive therapies. We would hope that with the use of more advanced preclinical models to help guide trial design that in time we may be able to find a role for such agents. We have included some discussion of this in the text.

We agree with the reviewer that we have not clearly established that E7080 inhibits invasion via an effect on PDGFR and have modified the text in line with
their suggestion.

Minor Revisions
Details on how the invasion assays were performed have now been included in the Methods section.

Discretionary Revisions
1. The last sentence in the abstract has been replaced in line with the reviewers comment
2. The reference described FGFR amplification in lung squamous cell carcinoma has now been included.
3. The cultured cells have been validated at the Beatson Institute biological services.
5. As discussed above we have amended the discussion with respect to the potential clinical use of anti-invasive agents.