Author's response to reviews

Title: Chk1 Inhibition as a Novel Therapeutic Strategy for Treating Triple-Negative Breast and Ovarian Cancers

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Author's response to reviews: see over
Response to Reviewer’s Report

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Reviewer 1 (Brian Gabrielli)

Minor Essential revisions: The authors need to more closely proof their manuscript. A number of the references are incomplete and in the Table provided, MDA-MB-453 is mislabeled as a luminal cell line.

We have checked the reference from which this information was taken and Neve et al have classified MDA-MB-453 as luminal hence we have not changed the table. We have proof read the manuscript and corrected any errors.

We have added some comments on the loss of Chk1 protein observed with higher doses of V158411 to the discussion.

Reviewer 2 (Ratna Vadlamudi)

1. It will be useful if authors add more information on the new drug V158411 in the introduction and discusses the differences between new drug with exiting CHK inhibitor drugs.

We are currently preparing another manuscript that will detail the discovery of V158411 and will describe the in vitro and in vivo pharmacology in much greater depth. This will compare V158411 to existing, published Chk1 inhibitors such as LY2603618, MK-8776, AZD7762 and PF-477736. It is quite difficult to summarise this in a few sentences in the introduction here.

We have moved the text “V158411 is a potent, selective inhibitor of recombinant Chk1 and Chk2 kinases in vitro with IC_{50} of 3.5 and 2.5nM respectively [29]. In p53 defective HT29 cells, V158411 inhibited the etoposide induced auto-phosphorylation of Chk1 on Ser296 with an IC_{50} of 48nM and Chk2 on Ser516 with an IC_{50} of 904nM indicating a 19-fold cellular selectivity for Chk1 over Chk2. V158411 potentiated cytotoxic chemotherapy in p53 defective cancer cells in vitro and in vivo.” from the results section to the introduction.
2. Earlier published studies showed efficacy of CHK inhibitor AZD7762 on breast cancer cells. The studies presented here using V158411 further extends these findings with new additional information. It is recommended to mention earlier published studies using breast cancer cells with other chk inhibitors briefly in the discussion.

The two main references relating to AZD7762 in breast cancer are Tang et al, Mol Pharmacol 2012 and Booth et al, Cancer Biol Therap 2012 but focus on the combination of CHK1 inhibition with PARP inhibition. We have added a comment on these papers to the discussion on P9, line 20.

3. Text needs proof reading and few references are incomplete. For ex. Ref #41, 37, 32, 33.

We have proof read the manuscript and corrected these references.

4. The quality of the figure 4 is not good and conclusions drawn are not well supported by the data presented. This figure quality need to be either improved, quantitated or alternatively can be deleted.

We have deleted Figure 4 (and text referring to it) and renumbered the other figures.