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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Version: 2
Date: 1 May 2014

Author's response to reviews: see over
Dear Editors,

Please find enclosed a copy of our manuscript, "Chk1 Inhibition as a Novel Therapeutic Strategy for Treating Triple-Negative Breast and Ovarian Cancers" by Bryant et al., which we would like to submit for publication as a Research Article in BMC Cancer.

Chk1 inhibitors have been extensively studied as potentiators of cytotoxic chemotherapeutic agents and are currently undergoing development in the clinic in combination with drugs such as gemcitabine, irinotecan and cisplatin. Recent studies have started to uncover specific cancer cell types where Chk1 inhibitors exhibit significant single agent activity. In this manuscript we identify, for the first time, triple negative breast cancer and ovarian cancer as such cancer types where Chk1 inhibitors, used as single agents, may be a rational therapeutic strategy for these difficult to treat tumours.

Triple negative breast cancer cell lines and ovarian cancer cell lines exhibited increased sensitivity to the novel and selective Chk1 inhibitor V158411 compared to breast cancer cell lines of luminal origin or derived from other, non-breast solid cancers. V158411 treatment increased DNA damage in these cell lines and induced apoptotic cell death. Protein expression profiling identified high levels of Chk1 phosphorylated at serine 296 in triple negative breast cancer cell lines and might provide a suitable biomarker for selecting sensitive patient populations. We speculate that underlying deficiencies in DNA repair due to the "BRCAness" of this cancer may be the mechanism responsible for the sensitivity of this cell line to Chk1 inhibition.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to the BMC Cancer. All authors are either current or past employees of Vernalis R&D Ltd and undertook these studies as part of their employment; CB and RR as part of their one year, undergraduate year-in-industry scientific training placement at Vernalis. AJM is a stock option holder of Vernalis R&D Ltd.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Andrew J. Massey PhD