Author's response to reviews

Title: Antitumour activity of a potent MEK inhibitor RDEA119/BAY 869766 combined with rapamycin in human orthotopic primary pancreatic cancer xenografts

Authors:

Qing Chang (qchang@uhnres.utoronto.ca)
Mark S Chapman (MarkSChapman@san.rr.com)
Jeffrey N Miner (JMiner@ardeabio.com)
David W Hedley (david.hedley@uhn.on.ca)

Version: 2 Date: 6 September 2010

Author's response to reviews: see over
September 6, 2010

Dear Dr Satdarshan P.S. Monga

Re: Manuscript #: 8804206144086522
Antitumour activity of a potent MEK inhibitor RDEA119/BAY 869766 combined with rapamycin in human orthotopic primary pancreatic cancer xenografts
Qing Chang, Mark S Chapman, Jeffrey N Miner and David W Hedley

We appreciated the review of this manuscript and the associate editor’s very useful suggestions and comments. We have addressed the suggested comments, and incorporate the reviewer and editor’s comments in a revised manuscript as detailed below:

Reviewer #1 (Remarks to the Author):

Chang et al have posed a well-constructed question on the efficacy and biological impact of a novel MEK inhibitor RDEA119. The study is well done, methodologically sound and presented clearly. The model system the authors use is primary human pancreatic cancer xenografts. The presented data demonstrate that RDEA119 is superior to rapamycin treatment in control of tumor growth in 2 of 3 models. The histology/IHC presented and the molecular analyses are well done with demonstrable differences between treatment groups and control. The authors also evaluate plasma PK of RDEA119. The manuscript was written clearly and the figures are annotated well. Overall the study is acceptable pending minor essential adjustments as indicated below:

1. Please indicate in the methods and legend of Figure 2 when therapy was initiated compared to when tumor were implanted.

We include the line “Due to the different growth rates of these 3 models, the drug administration was initiated on Day 52, 24, and 12 after implantation in OCIP19, 21, and 23, respectively.” in the methods and legend of Figure 2 (highlighted in yellow).

2. Please indicate in the legend of Figure 3 that the flow cytometric analyses were conducted from primary tumors, as currently written it is not obvious if the analysis is from cells grown in vitro or from tumor isolates.
We indicated in the legend of Figure 3 that “cell cycle effects following chronic dose administration of 3 orthotopic primary pancreatic cancer xenografts” (highlighted in yellow).

Reviewer #2 (Remarks to the Author):

This is a well-written, sound report that could have impact on the field. The question posed by the authors is well defined, and the methods used are appropriate and well described.

Discretionary revisions

1. A brief description as to why the oral dosage in addition to the intraperitoneal injection was necessary for this compound would be useful for those of us not familiar with this agent.

RDEA119 is orally active, whereas rapamycin (and its analogues) requires parenteral administration. We added a short statement (highlighted in yellow) at the top of Page 5.

2. While the cell cycle figure has all the pertinent data to support the authors’ conclusions, the way it is presented made it a bit difficult to follow the conclusions. Perhaps clearly labeling the G1, S, G2/M percentages may make it easier to appreciate the changes the authors saw.

We agree with this comment, and modified the figure accordingly.

Associate Editor's comments:

The manuscript is of interest to BMC-Cancer. Study is well thought and well-conceived. The results are clear and manuscript is well written and organized. There are minor comments raised by reviewers which will further improve the quality of the report. There is a competing interest which is not declared. The second author of the manuscript is an employee of Ardea Biosciences which is the supplier of the drug that is tested. This should be declared and resolved as necessitated by the BMC Cancer policies.

We declared that the second and third author of the manuscript were employees of Ardea Biosciences in the competing interests section, as required by the Associate Editor.

We hope that you will agree that we have responded adequately to these comments, and look forward to hearing from you.

Yours sincerely

David W. Hedley MD
Professor of Medicine, Laboratory Medicine and Pathobiology, and Medical Biophysics
University of Toronto
610 University Ave. Toronto ON M5G 2M9
t.416-946-2262 f.416-946-6546 email david.hedley@uhn.on.ca