Author’s response to reviews

Title: A Multicenter Phase II Study of Everolimus in Patients with Progressive Unresectable Adenoid Cystic Carcinoma

Authors:

Dong-Wan Kim (kimdw@snu.ac.kr)
Do-Youn Oh (ohdoyoun@snu.ac.kr)
Seong Hoon Shin (ssh1533@hanmail.net)
Jin Hyoung Kang (jinkang@catholic.ac.kr)
Byoung Chul Cho (cbc1971@yuhs.ac)
Joo-Seop Chung (hemon@pusan.ac.kr)
HyeJin Kim (yk503@hanmail.net)
Keon Uk Park (kupark@dsmc.or.kr)
Jung Hye Kwon (kwynjhye@naver.com)
Ji-Youn Han (jymama@ncc.re.kr)
Mi-Jung Kim (77kmj1012@hanmail.net)
Yung-Jue Bang (bangyj@snu.ac.kr)

Version: 4
Date: 16 October 2014

Author’s response to reviews: see over
October 14, 2014

Dr. Emily Crow

*BMC Cancer* Editorial office

Re: MS 1985681127128586

Dear Dr. Crow,

We thank the editors and reviewers for taking their time to review our submitted article entitled: “A *Multicenter Phase II Study of Everolimus in Patients with Progressive Unresectable Adenoid Cystic Carcinoma*”. We have revised the manuscript based on the reviewers’ comments and editorial requests. We have summarized the changes to the manuscript below, along with our responses to specific comments & requests.

All of the named authors have agreed on the submission of the revised manuscript. We hope that the revised manuscript will better meet the requirements of *BMC Cancer* for publication. We thank you again for the constructive comments.

Sincerely yours,

Yung-Jue Bang
Professor, Department of Internal Medicine
Seoul National University College of Medicine
101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea
Phone: +82-2-2072-2390
Fax: +82-2-764-2199
E-mail: bangyj@snu.ac.kr
Response to the Reviewers’ Comments and Editorial Requests

REVIEWER COMMENTS

Reviewer #1 (Mark McKeage):

This is a high quality report of a well conducted clinical trial of a therapy previously unstudied in this disease setting. It is suitable for publication as is without revision but could be improved by revision to address the following questions. The authors could make mention of myb translocations in adenoid cystic carcinoma and whether or not the resulting aberrant signaling would be suppressed by everolimus.

Answer: Thank you so much for the interesting suggestion regarding possible activity of everolimus in myb dependent tumors. Unfortunately, we could not find any data on the \textit{in vitro} activity of everolimus in myb driven cancers in literature.

The authors should comment on whether or not their findings are sufficient for justifying further clinical trials of everolimus in this setting and what the next clinical trial should be.

Answer: We have mentioned about the future clinical trials in the ‘CONCLUSIONS’ section as below;

\textit{“Trials of novel combinations of everolimus with other targeted agents are warranted”} (line 226-227)

Reviewer #2 (Filippo FDB de Braud):

PFS at 4 mos it is a very unusual end point even for this disease in a phase II study we wish to have prove of activity. PET FdG is not a proper way to evaluate ACC

Answer: Thank you for the relevant comments on the efficacy evaluation methods in our study. We also hoped that everolimus could make shrinkage of tumors. However, based on the prior clinical trials results, we expected that objective responses would occur in very limited numbers of patients. So, we put the 4-months PFS as the primary end-point of this study. We agree that the metabolic responses evaluation with FDG-PET is an experimental approach rather than a standard way for efficacy evaluation.

There are at least 3 experiences showing Recist responses with target agents in ACC

Revision: We have changed the line 219-220 according to your kind comments.

(Original) \textit{However, no single targeted agents produced objective responses in patients with advanced ACC.}

(Revised) \textit{However, objective responses to targeted agents are rarely observed in patients with advanced ACC.}
EDITORIAL REQUESTS

1. Ethical approval - Please update the Methods section of your manuscript to include the name of the ethics committee that approved your study. We recommend the following format: This study was approved by the ethics committee of [xxx] Hospital [or University]. If more than five ethics committees approved your study, you may wish to list the names of the committees in an additional file.

Revision: We have changed the description of the ethics committees in METHODS section per editorial request.

(Original) .. and approved by the local institutional review boards (IRBs) of each hospital.
(Revised) .. and approved by the local institutional review boards (IRBs) of Seoul National University Hospital, Kosin University Gospel Hospital, Catholic University Seoul St. Mary’s Hospital, Yonsei Cancer Center, Pusan National University Hospital, Seoul Veterans Hospital, Keimyung University Dongsan Hospital, Hallym University Medical Center, and National Cancer Center in Korea.

2. CONSORT study - As part of the process of revising your manuscript we would like to use the WebCONSORT tool which is designed to help you improve the reporting of your randomized trial. You can access the tool by clicking on the following link: http://www.webconsort.fr/registration.php?v0=E28DZac. Please be aware that by clicking on this link, your manuscript may be part of a research study. The researchers will have access to the revised manuscript but all details of the manuscript content and the identity of its authors will be treated confidentially. Participation in this study does not impact on any future acceptance or rejection of your manuscript.

Answer: The WebCONSORT tool cannot be applied to this study because it is a non-randomized trial.