Author’s response to reviews

Title: c-Met in esophageal squamous cell carcinoma: an independent prognostic factor and potential therapeutic target

Authors:

Yohei Ozawa (ozawa.youhei@opal.plala.or.jp)
Yasuhiro Nakamura (yasu-naka@patholo2.med.tohoku.ac.jp)
Fumiyoshi Fujishima (ffujishima@patholo2.med.tohoku.ac.jp)
Saulo J.A Felizola (felizola@med.tohoku.ac.jp)
Kenichiro Takeda (takeda.kenichirou@me.com)
Hiroshi Okamoto (qq4b2ev9k@beach.ocn.ne.jp)
Ken Ito (fafafapdx2000@yahoo.co.jp)
Hirotaka Ishida (hirotaka_1106@yahoo.co.jp)
Takuro Konno (supo4bowling9@yahoo.co.jp)
Takashi Kamei (tkamei@med.tohoku.ac.jp)
Go Miyata (miyata5@chuo-hp.jp)
Noriaki Ohuchi (noriaki-ohuchi@med.tohoku.ac.jp)
Hironobu Sasano (hsasano@patholo2.med.tohoku.ac.jp)

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Author’s response to reviews: see over
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Dafne Solera
Editor-in-Chief
BMC Cancer

Dear Drs. Dafne Solera and Jochen Lennerz (the reviewer of our manuscript):

We appreciate your comments on our manuscript entitled “c-Met in esophageal squamous cell carcinoma: an independent prognostic factor and potential therapeutic target.” We have revised the manuscript as per your recommendation. Please find our detailed responses to your comments enclosed herewith. Our responses are presented in bold, and the changes within the manuscript text are in red.

We hope that the revised manuscript is acceptable for publication in *BMC Cancer*. If you have any questions and/or comments regarding the revised manuscript, please do not hesitate to contact me.

I look forward to hearing from you soon.

Yours truly,

Yohei Ozawa, M.D.

Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine

1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
E-mail: ozawa.youhei@opal.plala.or.jp
Tel: +81-22-717-7214
Fax: +81-22-717-721
Minor Essential Revisions

1) Page 8, lines 116-117: ROC curve methodology. Please use wording as stated in the rebuttal.

to explain that the authors took patient survival into account to determine the actual H-score cut-off.
The authors may want to discuss the limitations of this approach with one brief sentence

Authors' response: Thank you for your comment. We have revised ROC curve methodology in “Methods” and added limitations of this approach in “Discussion” sections as follows:

Lines 116–120: We also determined the optimal cut-off values using the receiver operating characteristic (ROC) curve method, which indicated that “40” was the optimal cut-off for patients’ survival outcome when analyzing c-Met and HGF immunohistochemistry results (c-Met: 40.2, HGF: 40.8). It was also close to the optimal cut-offs for tumor depth (c-Met: 42.8, HGF: 40.2) and lymph node metastasis (c-Met: 55.0, HGF: 36.2).

Lines 272–273: However, these results might be challenging to analyze because the cut-offs were determined via patients' survival.

2) The compound applied does not inhibit the rearrangement (page 20/21 lines 326/327).

Please revise and clarify that there are other protein targeted by the compound (=gene products) ALK, ROS1.
The authors can check www.proteinatlas.org for ALK-staining in normal esophagus that looks fairly similar to their “high expression.”

Authors' response: Thank you for your comment. We have revised our manuscript as follows:

Lines 330-331: PF-2341066 is also known to inhibit the protein activation processes resulted from gene rearrangement of anaplastic lymphoma kinase and ROS1 tyrosine kinase [42, 43] in addition to c-Met inhibition.

3) Table 1 smoking and alcohol
The authors should add an "o" in history.

Authors' response: Thank you for your comment and we apologize for the error. We have added an “o” in the word “history.”

Discretionary Revisions
In Figure 4 and Figure 5 the statistical comparison bars/stars are a little confusing. Please consider the same approach as in your Figure 7A, i.e., to highlight the key comparisons (which I like a lot).

Authors' response: Thank you for your suggestions. We have changed the color of statistical comparison bars/stars according to cell lines in Figures 4 and 5 in order to highlight the appropriate comparison. (And the bars of Figure 7A used transparent color to highlight the Figure 7B.) In addition, we have revised the “Figure legends” as follows:

Figure 4: Green statistical comparison bars and stars represent the KYSE170 cell line.
Figure 5: Blue and red statistical comparison bars and stars represent the KYSE150 and KYSE180 cell lines, respectively.