Author's response to reviews

Title: Tumour Shrinkage at 6 weeks Predicts Favorable Clinical Outcomes in a Phase III Study of Gemcitabine and Oxaliplatin with or without Erlotinib for Advanced Biliary Tract Cancer

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Journal Editorial Office
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RE: MS: 1369783818128306- Tumour Shrinkage at 6 weeks Predicts Favorable Clinical Outcomes in a Phase III Study of Gemcitabine and Oxaliplatin with or without Erlotinib for Advanced Biliary Tract Cancer

Dear Editor-in-Chief

Our revised manuscript entitled, “Tumour Shrinkage at 6 weeks Predicts Favorable Clinical Outcomes in a Phase III Study of Gemcitabine and Oxaliplatin with or without Erlotinib for Advanced Biliary Tract Cancer” is enclosed for consideration for publication as an original article in BMC-CANCER. Our responses to the reviewers are detailed below.

I am looking forward to hearing favorable response from you soon.

Best Regards,

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# Reviewer 1

Biliary tract cancer is a relatively rare cancer and especially larger trials in molecular markers and newer targeted agents are much needed. This article is based on a previously published randomised trial comparing combination chemotherapy alone or with erlotinib. In the manuscript, the authors explore a new endpoint, tumour shrinkage at 6 weeks, as a potential clinically meaningful marker in the systemic treatment of biliary tract cancer. KRAS mutation and the treatment with erlotinib are included as variables.

Major Compulsory Revisions:

1) Only 103 out of 268 patients were included. There is a high risk of selection bias that cannot be corrected for.

# ANSWER

Thank you for your comments. I agree on your opinion. We added this limitation to the part of "Discussion"
The comment is as follows;

“This analysis was available in only 103 out of 268 patients who had been enrolled in our phase III trial. Moreover, the subgroups were relatively too small. Small sample size and selection bias of the current study may make definitive conclusions difficult.”

2) The inclusion of KRAS as a marker in biliary tract cancer is not justified. It is neither an established prognostic factor nor a predictive factor for effect of erlotinib.

# ANSWER

Thank you for your comments. I agree on your opinion. Thus, in the part of Discussion, we mentioned the KRAS as a biomarker in BTC.

“Although KRAS mutations are associated with less efficient EGFR-directed targeted therapy in various cancer types, it is not yet known if the same is true in BTC.[21, 22] Previously, we assessed whether the KRAS status could act as a predictive biomarker in patients with advanced BTC who received erlotinib, and this suggested that the KRAS mutation might be a predictor of resistance to small-molecule EGFR inhibitors. However, in present analysis, GEMOX plus
erlotinib group included only 5 patients with KRAS mutant tumor. Thus, we could not evaluate the role of KRAS status as a biomarker to erlotinib.”

Minor Essential Revisions:

1) In the introduction lines 74-78 the interpretation of the results from the randomised trial is overoptimistic and not according to good statistical practice.

# ANSWER
Thank you for your comments. I agree on your opinion.
I corrected the sentence in the part of “Introduction”.
Corrected sentence was as follows; “These findings suggested that the addition of erlotinib to GEMOX might be considered as one of treatment options for BTC patients, although the difference in PFS between the groups was not significant.”

2) Please check the definition of PFS in ‘Statistical analysis’. Was survival and not just progression included as an event?

# ANSWER
Thank you for your comments
“Progression free survival (PFS) was defined as the time from date of first study treatment to date of first documented disease progression or death”

3) Due to small numbers (only 8 KRAS mut), the speculative phrases in the abstract, discussion and conclusion about ETS as a marker for adding erlotinib in KRAS wt are not justified.

# ANSWER
Thank you for your comments. I agree on your opinion.
This analysis had some drawbacks such as small sample size, and selection bias.
Thus, our results must be interpreted with caution.

In the part of abstract and conclusion, we added the sentence as follows;
“These findings need to be prospectively validated.”

In the part of discussion, we added the sentence as follows;
“Small sample size and selection bias of the current study may make definitive conclusions difficult.
The rarity of BTC hinders clinicians from conducting definitive trials and from producing rigorous scientific data. Thus, coordination of trials among institutions and cooperative groups, both nationally and internationally, will be the key to improving treatment outcomes in BTCs.”
We appreciate the thoroughness of the reviewers and hope that these changes adequately address their concerns. These changes were indicated with red in the revised manuscript.