Author's response to reviews

Title: Complete response in gallbladder cancer to Erlotinib plus Gemcitabine does not require mutation of the epidermal growth factor receptor gene: a case report

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Author's response to reviews: see over
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Dear BMC Cancer Editors:

Re: MS: 2132589838408653

This letter addresses the reviewers’ concerns on our submission to BMC Cancer entitled, “Complete response in gallbladder cancer to Erlotinib plus Gemcitabine does not require mutation of the epidermal growth factor receptor gene: a case report,” by K. Mody, et al.

Reviewer 1:

1) Further discuss the effects of single agent gemcitabine in BTC.
   a. We corrected our original manuscript to reflect the fact that in the large randomized trial of gemzar vs. gem/cisplatin in BTC, there were no complete responses seen in gallbladder cancer patients; the two complete responses seen were only in patients with cholangiocarcinoma. (see Conclusion, first paragraph)
   b. We referenced two additional studies of single agent gemcitabine for the treatment of gallbladder and BTC; these also observed no complete responses. (see Conclusion, first paragraph)
   c. These references, plus our inability to find in the literature a single complete response of gallbladder cancer to single agent gemcitabine make us feel comfortable with our wording that it is “unlikely” that our patient’s CR was due solely to gemcitabine. (see Conclusion, third paragraph)

2) Provide a picture of FISH testing for EGFR amplification.
   a. Figure 4 has now been added to include the FISH testing and a new figure legend has been added to the manuscript.

3) Since a recently published article in the JCO (see below) tested EGFR mutations and made correlations with patient outcomes to treatment with erlotinib and bevacizumab, we should not state that our manuscript is “the first” to do so.
   a. In JCO 2010, 28: 3491-3497, Lubner et al tested BTC specimens for mutations in exon 1 (EGFR variant vIII) and polymorphisms in intron 1. They did not report on the mutation status of the EGFR tyrosine kinase domain (exons 18-21), which is the target of erlotinib.
   b. We have added “tyrosine kinase domain” of the EGFR gene to both the abstract and end of the background section to clarify the molecular specificity of the EGFR mutation tested.
   c. Our manuscript still represents the first report of tyrosine kinase domain mutation status and therapeutic outcome in BTC treated with a TKI; this
wording has, therefore, been kept in the manuscript (see end of the background section).

Reviewer 2:
1) What about the frequency of mutation of EGFR in gallbladder cancer?
   a. This data has been added to the manuscript (see Conclusion, fourth paragraph). “In BTC, a 13-15% tyrosine kinase domain mutation rate has been reported…”
   b. Two references (16 and 17) have now been cited regarding the above data.

2) Check figure 3 for mutation analysis.
   a. The submitted figure 3 does represent a PCR amplification plot of EGFR wild type sequences for the patient’s tumor specimen.
   b. The figure 3 legend has been modified to better reflect this.

We hope you find that we have adequately addressed the concerns of the two reviewers and that our manuscript is now suitable for publication in BMC Cancer.

Thank you so much for your consideration of our manuscript.

Respectfully submitted,

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