Reviewer’s report

Title: ERBB2, but not EGFR, mutations in hepatocellular carcinoma may predict response to EGFR-targeted therapy

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Reviewer: Balazs Halmos

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General
Bekaii-Saab et al report the results of a study looking at EGFR and ErbB2 mutations in tumor specimens from patients with hepatocellular cancer and biliary cancers. They claim the identification of novel ErbB2 mutations in 2/18 hepatocellular cancer specimens and conclude that these new mutations might predict responsiveness to EGFR-targeted therapy in hepatoma.

While their study goals are relevant and the results could potentially be interesting, there are a number of issues, such as the limited scope of the study, lack of in vitro confirmatory studies and lack of correlation with clinical response that limit enthusiasm for the ready acceptance of their conclusions.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Their title, abstract and conclusions all state that the ErbB2 mutations they identified “may predict”, “may be germane in predicting”, “may underlie responsiveness” to EGFR tyrosine kinase inhibitor therapy. I believe such statements are unfounded and misleading— they do not provide any information, either from clinical data or in vitro testing that would suggest that this is indeed true. In fact, ErbB2 mutations identified in non-small cell lung cancers are felt to be relatively refractory to EGFR TKIs. I believe these statements should be appropriately restated as speculation and in particular the title should be changed.

2. The methods section should be described in more detail. Were the specimens paraffin-embedded? How was DNA extracted? Were the tumors microdissected? What were the normal controls that they used? Normal liver for all (that seems to be the case at least for one of the mutants as shown in the figure)? PBMCs? Were the normal specimens processed the same way as tumor? E.g. Paraffin-embedding can lead to PCR artifacts due to deamination of DNA. They do not list what primers they used for ErbB2 sequencing. They state they did double-stranded sequencing for EGFR- did they do the same for ErbB2? If so, was the H878Y mutation confirmed in both directions?

3. The identification of such a novel mutation would certainly be of interest but the validity of their findings should also be further strengthened by subcloning the DNA and/or confirming the same mutation in RNA to mitigate the concern that it might just represent an artifact due to paraffin-embedding (assuming the specimens were paraffin-embedded). They state that they used 44 lung cancers as controls but do not describe the ErbB2 sequencing results on those samples— were ErbB2 mutations identified in those?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

1. The H878Y mutation they report in 2 hepatoma specimens are hypothesized to affect function but no attempt is made to confirm this in in vitro assays. Given the fact that these would represent novel mutations not described before, the functional consequences cannot be well predicted at this point without such studies and their conclusions would be greatly strengthened by such.

2. No clinical information is provided on the 2 patients whose tumor contained an ErbB2 mutations— it would be interesting to learn if there were any particular clinical or pathological factors that might correlate with the presence of these mutations (e.g. gender, history of hepatitis/alcoholism/estrogen use etc...). If such clinical data is available, it should be provided.
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests