Reviewer’s report

Title: Genetic predictors of cetuximab-based treatment activity in metastatic colorectal cancer

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Reviewer: Alberto Bardelli

Reviewer’s report:

The identification of molecular determinants to anti-EGFR therapies based on the monoclonal antibodies (cetuximab and panitumumab) is a very active line of research. Accordingly a number of reports have previously addressed this issue suggesting that increased EGFR copy number and KRAS mutation are correlated respectively with response and resistance to cetuximab (and panitumumab) treatments. The work of Goncalves and colleagues addresses further this issue. Specifically the authors attempt to correlate (in a retrospective analysis of cetuximab-treated patients) three parameters (EGFR copy number, KRAS mutations, and the presence of the EGFR extracellular variant R521K) with clinical response. The results indicate that increased EGFR copy number and the presence of the R521K tend to correlate with response. The EGFR copy number increase does not reach statistical significance while the presence of the R521K variant does (p = 0.041). The presence of KRAS mutations tends to be negatively correlated with response but the data do not reach statistical significance.

The experimental approach is appropriate and the data are clearly presented. The only novelty of this work is related to the finding that the presence of the R521K variant is associated with cetuximab response in mCRC patients.

The main weaknesses are (Major Compulsory Revisions):

1) Small size of the patient cohort examined. The inclusion of additional patients will undoubtedly improve the statistical power of the study.

2) The lack of functional evidence that the R521K variant affects the binding of cetuximab to the EGFR or somehow influences the signaling activity of this receptor and its partners. Experiments on CRC cell lines (genotyped for the presence of the R521K variant) could help addressing this issue.

Additional points (Minor Essential Revisions)

The title is very generic, as the novelty is related to the data on the R521K variant this should be reflected in the title.

Table 3 is mainly a meta-analysis of previous work (from other groups) and would be more appropriately included in a review article. Main conclusion could be listed in the text.
Sample used for genetic analysis were all from primary tumors of the liver. This is important as it could affect the genetic analysis.

It seems implicit that the genetic analysis was performed on samples obtained from tumors that were not previously exposed to cetuximab. This should be stated more clearly in the text.

**What next?**: Accept after minor essential revisions

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

**Quality of written English**: Acceptable

**Statistical review**: Yes, and I have assessed the statistics in my report.

**Declaration of competing interests**:

'I declare that I have no competing interests'