Reviewer's report

Title: Putative contribution of Natural Killer cells in cetuximab treatment efficacy in first-line metastatic colorectal cancer patients.

Version: 1 Date: 29 January 2010

Reviewer: Federica Di Nicolantonio

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Maréchal et al. aimed to test the hypothesis that antibody-dependent cell-mediated cytotoxicity (ADCC) might be partly responsible for the efficacy of cetuximab, a chimeric monoclonal antibody directed against the human EGFR. The authors report that the CD56+ immune cells might contribute to cetuximab activity by antibody-dependent cell-mediated cytotoxicity (ADCC) and that their presence could represent a positive biomarker of response to cetuximab-based regimens.

While the methods are accurately described, the results would benefit from additional experiments and data analysis (see below), and the discussion is amenable to improvement.

MAJOR COMPULSORY REVISIONS

1) The authors should determine whether there is any correlation between the presence of KRAS mutations and the staining of CD56 positive cells.

2) Oncogenic KRAS mutations have been shown to preclude efficacy of EGFR targeted monoclonal antibodies in CRC patients as well as in CRC cellular models. In order to improve the relevance of their work, the authors could investigate whether the presence of KRAS mutations has an impact on the putative role of CD56 positive cells in ADCC. For example, they should compare cells without and with oncogenic KRAS (e.g. SW480 or SW837, that are KRAS mutant but do not carry alterations in other possible biomarkers, such as PIK3CA).

3) Cetuximab, the first anti-EGFR monoclonal antibody to be approved for clinical use for metastatic colorectal cancer, is a chimeric mouse–human monoclonal antibody, while Panitumumab (the second antibody in clinical use) is a fully human monoclonal antibody. The latter is thought to be less prone to elicit ADCC. Yet, the two drugs have displayed similar clinical efficacy in metastatic colorectal cancer, suggesting that ADCC might play a marginal role. This aspect should be mentioned in the discussion.

4) The authors should briefly discuss that the relatively small number of analysed samples might a represent a limitation to their conclusions.

5) In CRC, immunohistochemical based methods for other biomarkers of response to cetuximab (EGFR gene copy number or PTEN status) are currently
proving difficult to standardize. The authors should include a brief statement about the potential of translating their preliminary findings to clinical trial setting.

MINOR ESSENTIAL REVISIONS

6) Page 11, lines 25-26 The following sentence of the discussion paragraph has appeared in the abstract of a recently published review (Siena S., et al., J Natl Can Inst, Vol. 101(19): 1-17, October 7, 2009) “The realization that detection of positive EGFR expression by immunostaining does not reliably predict clinical outcome of EGFR-targeted treatment has led to an intense search for alternative predictive biomarkers”

The authors should acknowledge this in their revision.

7) Page 12 – lines The following sentence of the discussion paragraph has again been published in the abstract of the above mentioned review (Siena S., et al., J Natl Can Inst, Vol. 101(19): 1-17, October 7, 2009) “Tumor K-ras mutations, which may be present in 35%-45% of patients with colorectal cancer, have emerged as an important predictive marker of resistance to panitumumab or cetuximab treatment”. Rephrasing is suggested to avoid copyright conflict.

8) Although the manuscript is sufficiently well written, some editing would improve its quality; for instance see repetitions of verb “evaluate” on page 13 –lines 12-18.

9) Table and Figures.

Two distinct figures have been labelled as Figure 2. The authors should amend this in the figure legend and throughout the text.

MINOR POINTS

Page 6, line 14 – Space is missing between the following words: ‘tumors’ and ‘were’
Page 7, line 10 – check spelling of adverb ‘histologically’
Page 7, line 19 – sodium pyruvate (instead of pyruvate sodique)
Page 11, line 16 – delete extra punctuation mark at the end of sentence.
Table 2: please include hazard ratios.
Appendix, page 2, line 16: check spelling of ‘saturing’

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

Yes. I am listed as a co-inventor of a patent that describes the use of EGFR gene copy number as a potential positive biomarker for the selection of patients who might benefit from anti-EGFR antibody therapy.

- Patent WO 2006/108627 A1. Title: ANTI-EGFR ANTIBODY THERAPY BASED ON AN INCREASED COPY NUMBER OF THE EGFR GENE IN TUMOR TISSUES.