Reviewer's report

Title: Biomarkers of benefit from cetuximab-based therapy in metastatic colorectal cancer: interaction of EGFR ligand expression with RAS/RAF, PIK3CA genotypes

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Reviewer: Jeffrey Evans

Reviewer's report:

Pentheroudakis and co-authors have submitted a manuscript with their results of a number of biomarkers in a retrospective study of patients treated with cetuximab.

The authors are to be commended for their extensive studies and for identifying a significant number of patients and samples for their studies. However, this manuscript also has a number of weaknesses.

Major Revisions

1. The authors have performed a number of statistical analyses with significance values reported. However, it would have been helpful if they had stated in their methods what was their intended primary analysis and the proposed significant difference that they wished to observe, and estimated the sample size on that basis.

2. Patients were included who received cetuximab as 1st, 2nd, or 3rd line therapy. Outcome analysis, such as PFS or overall survival, will not be robust in such a heterogenous group. Although the authors attempt to overcome this limitation by using objective response to cetuximab as indicator of efficacy, this may be influenced by the chemotherapy backbone to what the cetuximab was added (ie oxaliplatin - containing versus irinotecan - containing regimens). These limitations should be acknowledged.

3. The samples that were used were archival sample specimens ie taken at diagnosis. It is conceivable that some of the biomarkers studies may have changed by the time that patients received 1st, 2nd or 3rd line therapy. If the authors wish to study predictive markers then ideally they would use tissue collected prior to the intervention rather that archival material. I acknowledge the difficulties in doing this in retrospective studies. Nevertheless the authors should comment on these limitations to their study.

4. The main criticism of this manuscript is that the authors wish to develop predictive markers of cetuximab efficacy, for which there is no clear unmet need. However most of the data they present is on prognostic factors, which adds very little to the published literature and is of lesser impact. Furthermore, they have performed multiple analyses (and so, inevitably, some reach statistical
significance with a P value of <0.05) including on whether the tumour is in the left or right side of the colon. Much of this is of no impact and should be removed, concentrating instead on predictive markers. There are too many subgroup analyses on prognosis and the manuscript should be more concise.

5. The discussion is too long and repetitive. In addition they add that the absence of a control arm with no treatment makes it less robust to speculate on the prognostic or predictive effect of the biomarkers studied - which is a surprising comment as it undermines their own studies!

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no financial competing interests. The first authors was a junior (training) member of staff under me many years ago. Otherwise, I have no non-financial competing interests.