Reviewer’s report

Title: FCGR2A and FCGR3A polymorphisms and clinical outcome in metastatic colorectal cancer patients treated with 1st line 5-fluorouracil/folinic acid and oxaliplatin +/- cetuximab

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Reviewer: Patricia de Cremoux

Reviewer’s report:

The paper presented by JB Kjersem et al, presented very interesting data on the analysis of FCGR2A & FCGR3A polymorphisms in patients with metastatic colon cancer treated by 1st line chemotherapy (5FU/folinic acid and oxaliplatin) alone or combined with EGFR-targeted antibodies (cetuximab). To date, some independent small series of patients in different clinical and different therapeutically context were published, indicating that these two functional FCGR gene polymorphisms, that may affect the killing function of immune effectors cells in patients treated by IgG1 antibodies, may be relevant in the prediction of response or efficacy of therapeutically IgG1 antibodies. However, the results remained discordant. In addition questions related to the predictive value of RAS mutation in patients with advanced colon cancer treated by EGFR antibodies remained questionable taking into account recent large clinical trials with different chemotherapy regimen and also recent data on the value as negative predictive biomarkers of activating RAS mutations other than KRAS exon 2 mutations. For these reasons, this paper is particularly relevant.

This paper is well written and well documented by numerous clear tables

This paper is acceptable for publication if the authors have responded to the major essential revisions with corrections:

Major Compulsory Revisions

1/ This paper analyses FCGR2A & FCGR3A polymorphisms in the context of metastatic colon cancer with and without KRAS exon 2 mutations These results are interesting since the paper showed that these KRAS mutation status in the context of NORDIC-VII trial is not predictive of response to cetuximab whatever will be the arm of chemotherapy regimen. This remains either in accordance and also contradictory of some recent published trials with similar or different chemotherapy regimen. The subject remains to be elucidated. In fact, even if the datas on KRAS status are not in front line, they represents in addition to BRAF status a major element of the analyse of this paper and it has to be completed.

In the NORDIC-VII trial (published in 2012), the authors analysed for KRAS gene only hot spots mutations of codons 12 and 13 (7 mutations analysed) .. These alterations represent the majority of KRAS gene mutations, however, recent papers demonstrated that “wt type RAS “colon cancer are defined by the absence of KRAS exons 2, 3 and 4 mutations and the absence of NRAS exons
2, 3 and 4 mutations. This represents 17% additional RAS mutations that are not negligible. The predictive value of non-response to EGFR antibodies targeted therapy is increased by these determinations as recently published in the PRIME study (with another chemotherapy regimen and panitumumab).

- The authors could precise in the material and methods section the KRAS exons (or codons) analysed in NORDIC-VII trial (they were indicated in the referred paper, however of major importance in this context)

- If it is possible for the authors, could they obtain KRAS exon 3 and 4 and NRAS exons 2, 3, 4 data’s in their series of patients and analyse them in their study?

- If not possible, could the authors clearly mention it in the material and method section, and largely discuss this point in the discussion section?

2 In the results section the authors showed that they observed a higher response rate in patients with FGFR2A R/R polymorphism when cetuximab was added either regardless to KRAS mutational status, and in the group of KRAS mutated tumours. However, as showed in table 3, we observed that the response rate of this group of patients is similar to those of all other groups with the exception of the group of patients with FGFR2A H/H polymorphism that is clearly lower. One conclusion could be that patients with FGFR2A H/H polymorphism have a significant decreased response rate in the group of patients treated without cetuximab. All other genotypes gave similar response rate with or without cetuximab, and with or without KRAS mutated tumour. Could the authors discuss these results?

Minor Essential Revisions

3/ / The authors could also include the recent references including the data of RAS (KRAS and NRAS) determination and response to EGFR antibodies

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests