Reviewer's report

Title: Clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer

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Reviewer: Javier Hernandez-Losa

Reviewer's report:

The authors propose an interesting retrospective study where analyze the impact of the mutation profile of (KRAS, BRAF, NRAS and PIK3CA genes) in 265 CCRm samples and correlate it with their follow up focusing in the impact upon anti-EGFR therapies.

The rational of the paper and the experiments performed are quite good, statistics analysis and tables are also presented with high quality improving the obtained results.

Nevertheless, I have some minor considerations that I would like to know with more detail.

The authors employed a multiplex assay kit that had been previously published with perfect correlation with a comparative arm (sanger sequencing). Comparing the results from both manuscripts with different number of patients, in the present study the patients got better results in terms of FPS and OS. These differences could be explained by the different anti-EGFR therapy?(Cetuximab or Panitumumab).

The authors show in the discussion part, that the frequency of the mutations (KRAS exon 3 and 4, and NRAS 2,3 and 4) is lower that other Western reports. The authors reflect a total of 12.1% meanwhile in the abstract refer that 34.1% of KRAS exon 2, 3.8% KRAS exon 3 and 4 and also 4.2% in NRAS mutant, resulting a 8% of mutant frequency without KRAS exon 2 in their population. Please comment this discrepancy.

On the above comment, the authors propose several explanation for this lower mutation frequency including technical issues. One of them is the sensitivity of the assay that refer 5-10% whereas other recent publication using HRM provide 12% of mutant in japanese population "High-throughput screening of extended RAS mutations based on high-resolution melting analysis for prediction of anti-EGFR treatment efficacy in colorectal carcinoma. Clin Biochem. 2014 Sep 28". Please comment this discrepancy in the discussion part.

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 have no competing interests