Reviewer's report

Title: Beyond KRAS mutation status: influence of KRAS copy number status and microRNAs on response to cetuximab in metastatic colorectal cancer patients

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Reviewer: Andrea Sartore Bianchi

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The manuscript by Mekenkamp et al. evaluated KRAS CNA and miRNAs in correlation to clinical outcome in mCRC patients treated with cetuximab in combination with chemotherapy and bevacizumab from the CAIRO2 Trial.

Even though such biomarkers are novel and of interest for prediction of response/resistance to cetuximab in mCRC, the setting that Authors chose for this retrospective analysis is not appropriate to this aim. Patients indeed received cetuximab in combination with chemotherapy and bevacizumab, so that a good clinical outcome can be due to the other components of the regimen associated to cetuximab. Conversely, an unfavourable outcome can be due to the detrimental effect of combining the two monoclonal antibodies, as it was reported by the same Authors in the NEJM paper, and not to lack of efficacy of cetuximab. Generally speaking, in order to drive meaningful conclusions about any association between a given biomarker and a therapeutic effect one should be confident that such therapeutic effect is attributable only to the candidate drug basing on the proposed rationale (ideally with a control arm). In the case of mCRC treated with anti-EGFR this can be achieved in the chemorefractory setting as in the papers by Karapetis et al. (cetuximab) or Amado et al. (panitumumab). Moreover, it should be noted that the cohort analyzed is really small and any association with proposed biomarkers should be taken with extreme caution (for example more solid data about association with miRNA from blood and outcome to cetuximab in an appropriate setting and in a much larger cohort were recently reported at the ASCO Meeting [Abst. 3532]).

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

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

Declaration of competing interests:

I received lecture fees from Amgen and Merck-Serono