Reviewer's report

Title: KRAS mutations: variable incidences in a Brazilian cohort of 8,234 metastatic colorectal cancer patients

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Reviewer: Timothy Price

Reviewer's report:

The authors present data from a large Brazilian KRAS registry of sorts which has its origins as a Merck funded KRAS program. The program has no relationship to prescribing anti-EGFR agents, as is the case for similar programs in other countries. It does however provide the opportunity to analyse a large data set as the authors have done. As such this data is of interest particularly to local specialists, and does confirm historic data for exon 2 KRAS mutations and that the ratios are similar in Brazil. Findings related to sex are also of interest.

There are some issues however that need responding to, as follows;

Although I understand that this database pre dates the recent all RAS WT data, it does lead to this now being somewhat out of date. The authors should at least note this significant shift in the RAS story with reference to recent publications eg PRIME and PEAK studies, together with early data from the FIRE study. Whether it is feasible to run the exon 3,4 and NRAS is also a question to be raised but given the funding implications it would be accepted that this may not be possible.

I accept that the female to male ratio is statistically different but I must say the numbers do not differ greatly. The hypothesis is however of interest and the discussion of this is novel. Clarification of the hypothesis may be useful however. Are the authors suggesting that estrogen has a different impact on receptors in the bowel, that is that ER alpha is dominant, ER beta as protective less so. Or is there a difference that then leads to a more at risk population. Also, if the hypothesis relates to the receptor in women, do the ratios change in menopause? Or does the drop in estrogen levels lead to difference response at the receptor level so that ER beta becomes dominant?

Of note, the male risk increasing with age is more straightforward from the references provided.

The references for relevance of initial findings of KRAS exon 2 MT as a predictor of resistance should include Karapetis et al NEJM as this is a definitive paper. G13D mutation rate as expected but not discussed.

Does the Southeast data from the “most developed” part of Brazil reflect clinicians submission of patients material, and therefore varies based on difference in numbers ie if the funding for agents also differs will there be a difference in relevance of the results?

Re prognosis, which is commented on in the discussion (ie unable to assess), it
is unfortunate that survival could not be assessed and I presume there is not a central cancer registry that could have been used for at least this outcome?

The authors comment on different rates of MT based on patient background, re this point, it may be useful to the reader to understand the general background of Brazil population. This is relevant when the authors reflect on data from Asia in the discussion.

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

**Declaration of competing interests:**

Advisory board member of AMGEN and MERCK