Reviewer's report

Title: Next generation sequencing of exceptional responders with BRAF-mutant melanoma: implications for sensitivity and resistance

Version: 1
Date: 29 August 2014
Reviewer: Jeff Holst

Reviewer's report:

This study examines DNA mutations by NGS in 10 BRAF mutation melanoma patients who have shown either partial response or complete response to BRAF and/or MEK inhibition. This is stated as a “pilot study”, and due to the corresponding low numbers of patients, there are no statistical analyses, which greatly limits application of these data. Especially in comparison to two new publications (Siroy et al JID 2014 - DOI: 10.1038/jid.2014.366 and Xia et al Molecular Cancer Therapeutics 2014 - DOI: 10.1158/1535-7163.MCT-13-0804), which study large melanoma cohorts.

The strength of this current study, however, compared to these larger cohorts is that it is focused on those patients that respond well to therapy. This allows the authors to dissect out which patients will respond best, as well as which other mutations may be targeted together with BRAF to enhance or prolong the response. The fact that two patients with low mutation burden are among the best responders justifies this approach and their conclusions. Although these data would have been predicted, it is an important finding.

The study would have greatly benefited from analysis and comparison of patients who did not respond – to determine whether their mutation burden is higher. This was acknowledged by the authors in the discussion, although the lack of this comparison makes it more difficult to determining the significance of the data from such a small population of patients.

As acknowledged by the authors, analysis of 10 patients, together with a great degree of tumor heterogeneity as well as molecular evolution of the individual patients tumor, also confounds the conclusions of this study.

- Minor Essential Revisions
  1 - Background lines 66-68 need a reference.
  2 - Background line 71 has a reference in an alternate superscript rather than [ ] style.
  3 - For patients that were BRAF V600E positive but were subsequently negative on NGS, confirmation of BRAF mutation status by PCR would be helpful, particularly for patient 3, as only two samples were analysed for BRAF mutation, and it would be important to ensure they were V600E positive.
  4 - Patient numbers should be added to Figure 1 for clarity.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:
I declare that I have no competing interests