Reviewer's report

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

Version: 1 Date: 9 June 2014

Reviewer: Rene Bernards

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The manuscript by Wheler et al describes the analysis of 10 patients having BRAF mutant melanoma. Biopsies taken pre-treatment with BRAF and/or MEK inhibitor were compared for mutation load by exome NGS. In addition, a number of biopsies were available upon progression. The authors conclude that patients having durable responses have no “actionable” mutations besides BRAF, suggesting that deep sequencing may be able to identify the group of patients that has lasting responses to BRAF/MEK inhibitors.

There are several issues that complicate the interpretation that the authors give for their finding:

First, the biopsies are very heterogeneous in terms of the time at which the biopsies were taken. Obviously, a biopsy taken 53 months prior to treatment will potentially be less heterogeneous than one taken 2 months prior to treatment, due to clonal evolution of the cancer. To allow any conclusions to be drawn, biopsies should be far more homogenous in terms of time to start of treatment.

Second, the authors have a rather liberal definition of “mutation of known significance”. This is presumably a Foundation Medicine definition (who did the sequencing work), but “significance” does not relate to significance in relation to BRAF resistance. For instance, NF1 mutation was recently shown to be causally involved in resistance to BRAF inhibitors. I would therefore define NF1 as “of known significance” for BRAF resistance. However, APC mutation has to the best of my knowledge not been implicated in resistance to the drugs used here and it is therefore not correct to label an APC (or PAX5) mutation as a mutation that has significance to drug resistance.

These issues make the manuscript short on results (88 text lines) and long on discussion (137 text lines). In a nutshell, this highlights the problem with this manuscript, there is a lot to speculate, but few solid data.

Level of interest: An article of limited interest

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'