Reviewer's report

Title: Exploiting high-throughput cell line drug screening studies to identify candidate therapeutic agents in head and neck cancer

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Reviewer: Steven Whittaker

Reviewer's report:

This manuscript describes the specific analysis of head and neck squamous cell cancer (HNSCC) cell line data generated from the large-scale studies performed by Barretina et al and Garnett et al. The authors sought to identify therapeutics with particular activity in HNSCC cell lines versus the entire cell line collections. Firstly, they confirmed that the mutational landscape HNSCC cell lines was representative of primary tumors, though the cell lines harbored additional mutations not nominated in the clinical data. The authors identified several drugs that displayed significantly lower IC50 values in the HNSCC cell lines versus the complete cell line collection, namely the BCR-ABL inhibitor bosutinib, the EGFR inhibitors BIBW2992 and gefitinib, and the microtubule-targeting agent docetaxel.

HNSCC cell lines with PIK3CA mutations, common in HPV-positive tumors, were also identified to be sensitive to PI3K inhibition.

- Major Compulsory Revisions

N/A

- Minor Essential Revisions

1. The authors should refer to a recent, complimentary study by Lui et al (Cancer Discov. 2013 Jul;3(7):761-9) where they describe the presence of PI3K pathway mutations in 30% of HNSCC tumors and the selective activity of BEZ-235 for PIK3CA-mutant HNSCC cell lines and patient-derived tumor xenografts and how PIK3CA mutation status may serve as a useful biomarker for treatment selection in HNSCC. Could the authors compare this with their findings where NVP-BEZ235 was not associated with a response in HNSCC?

2. Interestingly, the EGFR inhibitor erlotinib did not yield a significant response in HNSCC cell lines. Perhaps the authors could discuss the potential reasons for this inconsistency?

3. The authors highlight the presence of additional mutations in the HNSCC cell lines that are not observed in the primary tumors but do not describe these observations in detail and should comment on their potential relevance. In particular, the top-ranking mutated gene, NCAM1, appears to have a potential functional significance as it is known to signal through FAK, a direct target of
PF-562271, which may contribute to its activity in the PIK3CA-mutant HNSCC cell lines.

**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.