Reviewer's report

Title: Intratumoral heterogeneity impacts the response to anti-neu antibody therapy

Version: 4 Date: 24 April 2014

Reviewer: paul cottu

Reviewer's report:

- Major Compulsory Revisions
The authors should be cautious: they have a general trend along the manuscript to overinterpret the results. For example, they present no validation data supporting the assertion that TUBO-P2J invasion capacity may be attributed to MMP9 expression (e.g. knock out or SiRNA data). There is also no formal demonstration that the expression of mesenchymal markers is these cells is associated with an effective EMT process.

The heterogeneity chapter is difficult to understand as well. The authors present an experimental “heterogeneous” HER2+ tumor, based on a mix of TUBO and TUBO-P2J cells at 2 different dilutions. However and this is a critical limitation to their results, they present no data proving that HER2 expression is indeed heterogeneous in the resulting xenograft. A relationship between tumor cell dilution and extent of HER2 heterogeneity in the final tumor should also be established. These data are required before reconsidering the manuscript. Additional cell dilutions would be also welcomed.

- Minor Essential Revisions
Some typo here and there

The origin of the TUBO cell line should be indicated, for the sake of the readers who may not be familiar with the field. The authors should specify it has been derived from a transgenic mouse strain developing HER2+ murine mammary cancer.

IHC data are required for comparative HER2 status assessment in TUBO and TUBO-P2J cell lines.

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:
'I declare that I have no competing interests'