Reviewer's report

Title: Optimizing the Clinical Development of PI3K Inhibitors

Version: 3 Date: 27 August 2012

Reviewer: Hendrik-Tobias Arkenau

Reviewer's report:

The review by Bran et al focuses on how to 'Optimize the Clinical Development of PI3K inhibitors'. The review is well balanced and addresses important issues:

Major:

- The part 'Strategies to optimize the development of PI3K inhibitors' should be much more stringent, i.e. move away from pan-PI3K inhibitors to isoform specific inhibitors, improve understanding of tumour biology before Tx and while on progression, dosing schedules modification based on PK/PD data, in general patient/tumour selection (BRAF- i have different responses in melanoma versus CRC or thyroid cancer)
- Put the PI3K Isoform-specific inhibitors in order, ie. I, II, III
- Explain the difference between 1st generation PI3K alpha-specific and new PI3K alpha-isoform inhibitors
- One paragraph talks about the lack of response of KRAS and PIK3CA mutation to PI3K inhibitors - the results of BYL719 show that a KRAS/PIK3CA mt CRC is one of the responders - this would be a good opportunity to talk about tumor heterogeneity and that preclinical models often don't reflect the complex in vivo models.
- The part 'patient selection' should be more concise and shorter.
- Overall would recommend shorten the review to a max of 3000 words as some parts are repetitive, i.e. tumour biopsies on progression mentioned in several parts.

Minor:

- Minor spelling errors and grammatical changes necessary.

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