Reviewer's report

Title: Optimizing the Clinical Development of PI3K Inhibitors

Version: 3 Date: 10 September 2012

Reviewer: kyriakos papadopoulos

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Discretionary Revisions

In their paper, Brana and Siu provide a current review of PI3K isoform specific inhibitors in cancer therapy, highlighting the obstacles pertinent to the clinical development of these drugs and suggesting strategies on how these might be overcome.

As noted, the presence of a PI3KCA aberration in itself does not predict for sensitivity to PI3KCA inhibitors. Preclinical data suggesting resistance to BYL719 when PI3KCA and KRAS mutations coexist, appears contradicted by clinical response in a KRAS mutant colon cancer patient with a PI3KCA mutation. Just as with apparent differential sensitivity to BRAF inhibitors in BRAF mutant melanoma and colon cancer, the authors might consider some speculation on the possible relevance of histologic context with regard to both sensitivity and mechanisms of resistance.

With respect to patient selection for PI3K inhibitor studies, the authors posit data from Janku et al that patients with PI3KCA mutant tumors have a higher response rate when treated with PI3K-AKT-mTOR inhibitors than patients without this mutation. Of relevance, that warrants some comment, is that the majority of these patients received combination therapies that did not include a PI3K inhibitor.

In the discussion of dosing schedule and administration, the authors should mention that the majority of these drugs are administered orally, while others such as BAY 80-9646 and SF-1126 are given intravenously. These different modes of administration may be relevant not only to efficacy but also toxicity.

Minor Essential Revisions

Pg 3 “targeted agents such as BRAF..”
Pg 12 “ patient population most likely “
Pg 15 “ recurrence was induced .. by treatment with pan-PI3K inhibitor” - this is incorrect, recurrence was spontaneous and in some cases inhibited by treatment with pan-PI3K inhibitor.

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

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