**Author’s response to reviews**

**Title:** Clinical Development of PI3K Inhibitors for Cancer Treatment

**Authors:**

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**Author’s response to reviews:** see over
Dear Dr Arkenau,

Thank you for reviewing our manuscript. Your comments have been addressed and the pertinent changes have been incorporated in the manuscript.

Comment 1: “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)”

- We believe it is premature to state that isoform specific PI3K inhibitors are superior to pan-PI3K inhibitors, and as such stating to “stay away” from the latter is not entirely consistent with our view. We believe that we still need to see what the early phase clinical trial results are with the isoform specific inhibitors before one can make such a conclusion.

- We have added sentence about patient selection being enhanced by understanding the biological significant of PI3K pathway alterations – this is tumor type specific and may well be patient specific.

- We have added sentence about using PK/PD data to guide dosing schedules.

Comment 2: “Put the PI3K Isoform-specific inhibitors in order, ie. I, II, III”

- The PI3K isoforms have been put in order.

Comment 3: “explain the difference between 1st generation PI3K alpha-specific and new PI3K alpha-isoform inhibitors”
- A brief description about the difference between first generation of PI3K alpha-specific and new generation have been added.

Comment 4: “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.”

- A sentence has been added to the end of this paragraph addressing these points.

Thank you for your comments,

Irene Brana and Lillian L Siu.
Dear Dr Papadopoulos,

Thank you for reviewing our manuscript. Your comments have been addressed and the following changes have been performed in the manuscript.

Comment 1: “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”
- A paragraph has been added in page 8 to discuss this point.

Comment 2: “The authors might consider some speculation on the possible relevance of histologic context with regard to both sensitivity and mechanisms of resistance”
- A paragraph has been added in page 5 and page 14 to address this topic.

Comment 3: “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”
- A sentence has been added to clarify that most of the patients in this study received mTOR inhibitors and not PI3K inhibitors.

Comment 4: “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”
- A sentence has been added in page 16 to discuss this point.

The minor essential revisions in page 3, 12 and 15 have been addressed.
Thank you for your comments.

Irene Brana and Lillian L Siu.