

## Response to Reviewer #1

No.	Query	Response
1	I believe the manuscript is well written. It would benefit from minor language polishing.	The English language of the manuscript has been polished.

## Response to Reviewer #2

No.	Query	Response
1	The title of the paper is not accurately expressed, and I think it needs to be rewritten.	The title has been rewritten. (Page 1)  "Roles of PI3K Signaling Pathway in Inflammation-Related Cancer: Impact of rs10889677 Variant and Buparlisib in Colitis-Associated Cancer"
2	The following reference may increase the reader's comprehension: Sheikholeslami A, Fazaeli H, Kalhor N, Khoshandam M, Eshagh Hoseini SJ, Sheykhhasan M. Use of Mesenchymal Stem Cells in Crohn's Disease and Perianal Fistulas: A Narrative Review. Curr Stem Cell Res Ther. 2023;18(1):76-92. doi: 10.2174/1574888X16666210916145717. PMID: 34530720.	Thank you for the suggestion. This information will be relevant for my future studies.
3	It is better to include the results of the inflammation gene expression analysis, including IL-6 and IL-8.	This study is a continuation from the previous study conducted by our group that has identified SGK2 as one of the prominent genes in long-duration UC patients that have higher risk of developing CAC.  (Low, E.N.D.; Mokhtar, N.M.;Wong, Z.; Raja Ali, R.A. Colonic mucosal transcriptomic changes in patients with long-duration ulcerative colitis revealed colitis-associated cancer pathways. J. Crohns Colitis 2017, 13, 755–763.)  Thus, in this study, we attempted to keep the focus on the non-AKT downstream of PI3K signalling

		<p>pathway.</p> <p>Nevertheless, it was an excellent suggestion to include the results of the expression of inflammation related genes, which can be applied in the future study.</p>
4	In order to make the paper more interesting to read, I suggested that the authors could add one graphical abstract to the manuscript.	The graphical abstract has been included (Page 3).
5	I suggest including clear limitations of the study in the discussion.	The study limitations have been included in the discussion part (Page 17).

### Response to Reviewer #3

No.	Query	Response
1	Buparlisib has shown encouraging results in in vivo studies, and the conclusions reached in this study are no different from previous studies. Not much new overall. The mechanism of the down-regulation of PDK1 and SGK2 by Buparlisib needs further study.	<p>It is undeniable that PI3K has been linked to many others inflammation-related cancer. In fact, PI3K inhibitor, buparlisib also has been tested in multiple cancers cases. However, to date, the application of buparlisib in colitis-associated cancer has not been tested, specifically in the CAC-induced animal model.</p> <p>Furthermore, the present study did not cover an investigation into the specific mechanism underlying the down-regulation of PDK1 and SGK2 by Buparlisib. This is an excellent suggestion for the future continuation of this study.</p>