Dear reviewers,

Thank you for taking the time to review this manuscript.

Please see below answers to your comments:

Reviewer 1:

1. The readers should understand why KRAS-mutated pancreatic cancer is totally different from KRAS wild type. Please add some sentences in the Introduction section regarding the peculiarities of KRAS-wt pancreatic cancer.

We agree KRAS-wt is a very interesting topic and we are working on another review article that specifically discusses this unique subgroup in detail.

2. Please add some specific sentences regarding KRAS G12C (and related drugs, too) as a promising target in lung cancer patients (KRAS paragraph).

We only mentioned KRASG12C in lung cancer briefly, to point out a successful example. But did not expand on it as we believe it’s a heavily researched topic with multiple publications. Instead, we tried to focus on the role of KRASG12C in pancreatic cancer and new drugs that target this mutation like Sotorasib and Adagrasib.

Reviewer 2:

Thank you very much for inviting me to evaluate the mini reviews titled “Targeting KRAS in Pancreatic Adenocarcinoma - Progress in Demystifying the Holy Grail”. In this article the authors summarized some of the efforts made to target the KRAS pathway which plays an important role in cancer cell proliferation, differentiation, metabolism, and survival, making it an essential mutation for targeted therapy in PC, discuss the challenges, and shed light on promising clinical trials. The information in this review may be useful to clinical communities. The paper is well arranged and the logic is clear, and the provided figure and tables are well composed and understandable. The quality of language of the manuscript is quite acceptable for me. But this article has “obvious differences”:

1) Viewpoints involved in the article lacks a comprehensive discussion, and directly uses examples for discussion.

Our aim in this article was to give a simple overview of the advances in targeting the KRAS pathway with focus on its role in pancreatic cancer. A more detailed discussion will not allow us to cover the entire pathway, due to the large number of data available and clinical trials conducted. But future studies should focus on each step of this pathway and expand further.

2) The treatment methods mentioned explain the mechanisms, but do not give specific efficacy data, which is puzzling. So, I recommend that this manuscript may be accepted after major revision. Here is a question for the authors, Please systematically explain how KRAS mutations drive tumor progression and possible drug resistance mechanisms, which is an important part of the discussion on this topic?

Provided efficacy data when applicable, as some early phase I trials and pre-clinical studies don’t have efficacy data at this time.
Reviewer 3:

The authors discussed the KRAS and its pathway from basic research to clinical trials. The pathway including KRAS, MEK, ERK, PI3K, and so on has been studied a lot and the drugs targeted the pathway also been studied a lot, so now there are many ongoing clinical trials. Since it is a mini-review, it is fair that the authors only placed the full informations but not discussed a lot, therefore, this manuscript does not have enough novelty. The most important issue is who is going to be the audience of this manuscript.

We believe there is a large audience of researchers, clinicians, and oncology fellows that can use this article as a summary of information on targeting KRAS in pancreatic cancer that is collected from multiple clinical trials over the last few years. This will also be helpful for drug developers in the expanding field of precision oncology.

Best,

Authors