Response to reviewer's comments:

First of all, we'd like to thank you all reviewers for their positive and constructive comments and critics.

Reviewer ID: 02954661

Dear Editor, Thank you for the opportunity to review the interesting manuscript entitled 'Shattering the castle walls: Anti-stromal therapy for pancreatic cancer'. The authors reviewed the role of pancreatic cancer - peritumoral stroma interaction, and the therapeutic possibilities to increase the cytotoxic effects of current chemotherapy regimen targeting also peritumoral stroma. The paper has merits to be accepted after minor revision. Major concerns: - I suggest a table in which should be done a synthesis of the review; I suggest as columns: headings from the article, therapeutic stategies, current existing studies, etc. Minor concerns: In keywords: SPARC - pleas detail what means this abbreviation. In figure 1 - please detail all abbraviations. I recommend to authors our meta-analysis: 'Negoi I, Hostiuc S, Sartelli M, Negoi RI, Beuran M. MicroRNA-21 as a prognostic biomarker in patients with pancreatic cancer–A systematic review and meta-analysis. The American Journal of Surgery. 2017 Sep 1;214(3):515-24'. We found that 'The microRNA-21 upregulation was significantly associated with poorer overall survival, disease-free survival, and progression-free survival. The subgroup analysis revealed that microRNA-21 overexpression has a significant higher prognostic value for patients who receive adjuvant chemotherapy. Increased microRNA-21 was associated with a statistically significant higher rate of metastatic lymph nodes and poorly differentiated tumors.

Answer: After this comment, we had a chance to read Dr. Negoi's study. It was fantastic and as emphasized by Dr Negoi, the findings from the study are crucial for our manuscript. Therefore, we added their results about the relationship between microRNA-21 upregulation in tumor tissues and blood samples and poor clinical outcome to our review as follows: " A meta-analysis showed that miR-21 upregulation in tumor tissue and blood samples of patients with PC was significantly associated with poorer overall survival, disease-free survival, and progression-free survival. A significant correlation was detected between miR-21 expression and lymph node status and tumor grade [51"

Reviewer ID: 03471272

The review provided useful information related to anti-stromal therapy for pancreatic cancer. The manuscript would improve if the authors summarize pros and cons of stroma-targeting therapy. In addition, some points need to be added or revised before this paper can be considered for publication. 1. The authors should provide their own data. 2. It would be better to discuss other components of stroma (vessels, immune cells, etc). 3. The authors described "PSCs resemble myofaibroblasts"; therefore, it would be better to discuss difference between those cells. 4. It would be better to discuss the side effects of stroma-targeting therapy.

Answer to reviewer: Unfortunately, we don't have our own data. But, we are close follower of the literature data on pancreatic cancer stroma treatment. We discussed the differences between PSCc and myofibroblasts:

"PSCs phenotypically resemble myofibroblasts and exhibit the -smooth muscle actin expression. However, in contrast to myofibroblasts, PSCs are positively stained for selective markers such as desmin and glial fibrillary acidic protein. They also demonstrate increased proliferation and migration ability relative to myofibroblasts, and can produce large amounts of collagen and other ECM proteins [10, 11]."

We added some information about side effects of stromal therapies:

"PEGPH20 treatment was also associated with increased incidence and severity of other manageable side effects, such as painful muscle spasms, arthralgia, peripheral edema, and neutropenia." Since only PEGPH20 is about to use in clinical practice we discussed only its side effects.

As we have prepared a minireview, we have limited our discussion to some specific structural features of the pancreatic cancer stroma. In fact, the reviewer is certainly right, but stromal components of the pancreatic cancer have been discussed extensively elsewhere. Therefore, we did not include any information about vessels and immune cells etc. into our paper.

Reviewer ID: 03472014

The minireview by Ozkan Kanat and Hulya Ertas highlights role of stroma in the development and progression of pancreatic cancer (PC) and summarises the current status of anti-stromal therapies in the management of metastatic PC. The topic is of significant facet in the development of effective cancer therapy. This manuscript can be scholarly presented by having the following revision; 1. Research findings and literature on exosome-mediated PC progression by Pancreatic Stellate/Stroma Cells need to be reviewed. It is suggested to have these literatures presented to support the imperative role of stroma in cancer progression. 2. It has been shown that PSCs/Stoma plays crucial role in formation cancer stem cells (CSCs) which confers aggressiveness/invasiveness in tumour, hence a section on the mechanism of CSC induction and regulation by stoma will be intriguingly develop the discussion and knoledge around this topic. 3. Section on "Upregulation of microRNAs in PSCs": It is not clear on why the section focused on only miR-21. Is this the only microRNA implicated/upregulated? A comprehensive microRNAs list and mechanism implicated in this process will enhance the discussion. 4. It is suggested to provide a critical discussion on challenges and future perspectives as a section.

Answer to reviewer:

We added the results of studies on exosome-mediated PC progression by Pancreatic Stellate/Stroma Cells:

"Recent studies have shown that extracellular vesicles (also known as exosomes) derived from PSCs may play a role in the progression of PC [33, 34]. Takikawa et al. [34] reported that immortalized

human PSCs produce exosomes containing numerous microRNAs (miRNAs) that can induce chemokine gene expression in PC cell lines resulted in increased proliferation and migration. Leca et al. [35] found that annexin 6A/receptor-related protein 1/thrombospondin-1 complex-containing exosomes released by PSCs could increase PC cell aggressiveness under physiopathologic conditions. In addition, exosomes have been suggested to contribute to chemoresistance of PC cells by promoting reactive oxygen species detoxification and by decreasing gemcitabine-metabolizing enzyme activity [36]."

We discussed the relationship between stroma and stem cell induction in pancreatic cancer:

"Preclinical data indicated that PCSs might enhance stem-cell like phenotypes in PC cells [31]. Indirect co-culture of PSCs with PC cells increased the spheroid-forming capacity of tumor cells, and induced the expression of stem cell-related genes including Nestin, ABCG2 and LIN28 [31]. Lonardo et al. [32] showed that the secretion of transforming growth factor-β superfamily members Nodal and Activin from PCSs significantly promotes the self-renewal capacity and invasiveness of PC stem cells."

We discussed other microRNAs and their potential roles in pancreatic cancer progression:

Frampton et al. [52] reported that, in addition to miR-21, other miRNAs, such as miR-10b, miR-34, miR-155, and miR-203 also appear to have prognostic significance in pancreatic ductal adenocarcinoma. The dysregulation of miR-320a, miR-365, miR-200, and miR-210 has been found to be involved in tumor invasion, epithelial to mesenchymal transition development, and chemotherapeutic drug resistance in PC [53].