Response to reviewers

Reviewer's code: 01468039

We thank the reviewer for carefully reading our manuscript and for giving the positive comment.

Comment to authors: Well designed study.

We were pleased to receive that your classification of our paper was "grade B (Very good)".

Reviewer's code: 02543990

We thank the reviewer for carefully reading our manuscript and for giving detailed comments and suggestions.

Comment to authors: 1. It is not clear about the rationale for selecting BxPC-3 cell line in this study. BxPC-3 cell line carries wild type Kras, while most of pancreatic cancer cell lines have mutant Kras, which raises the concerns about the relevance and significance of this study. 2. Only one cell line was used in this study.

We agree to the reviewer's comments and concerns about only BxPC-3 cell line was used in our study. With using only one cell line, specific phenotypic characteristics and genotypic status of cell line may raise some limitation due to the lack of comprehensive comparative findings. Generally, several cell lines should be used in the kind of this study. Although we kept this point in mind, we started to work with BxPC-3 cell line only. Both *in vitro* and *in vivo* experimentation using one cell line remains a convenient starting point for discovery and proof-of-concept studies.

Other encouraging rationales for selecting BxPC-3 cell line in this study is its high expression of integrin α6β4 which is the specific binding-target of our radioimmunotherapeutic (RIT) agent ^{90}Y-ITGA6B4. In our previously published paper (*Aung et al.* Immunotargeting of integrin α6β4 for single-photon emission

computed tomography and near-infrared fluorescence imaging in a pancreatic cancer model, *Mol Imaging. 2016; 15*), we examined the expression levels of α6β4 in BxPC-3 cell lines by western blotting and flow cytometry, and we selected BxPC-3 as the representative α6β4-positive cell line. Moreover, we have studied the RIT effects of ^{90}Y-ITGA6B4 on the pancreatic cancer xenografts established by inoculation of BxPC-3 cells in nude mice (*Ref # 4, Aung et al.* Radioimmunotherapy of pancreatic cancer xenografts in nude mice using ^{90}Y-labeled anti-α6β4 integrin antibody, *Oncotarget. 2016; 7(25)*). Taken together, basing on the previous results, continuation to extend the our work with BxPC-3 cell line is timely and convenient for us.

We appreciated the reviewer's advice to think about the other pancreatic cancer cell lines with different genotypic status of commonly altered genes (eg. KRAS, p53). Although it would be worthy to obtain the more convincing evidence with larger variety of pancreatic cancer cell lines, it was unfortunately difficult to perform this study immediately because of time consuming procedure to prepare and the tight scheduling of experiments in our institute. We will resolve this issue in next study.

3. In Figure 5, quantitative and statistical results should be provided for the IHC analyses.

We agree to the reviewer's comments. In addition to Figure 5, we added the quantitative and statistical results of Ki-67 positive cells and p-H2AX-positive cells counts observed in immunohistochemical staining in Table 1. We amended accordingly some descriptions related to this point in the Materials & Methods (Page 12, Line 6-9, Line 14-15), Results (Page 14, Line 20, 21), Discussion (Page 18, Line 7, 9, 11), and Figure Legends (Page 28, Line 15-18, Line 20-22) of the revised manuscript.

Response to editor's suggestion;

We thank the editor for carefully reading our manuscript and for giving detailed suggestions. According to editor's suggestion we did the following tasks.

1. We provided our manuscript with word format (.docx).
2. We provided language certificate letter by professional English language editing company (Editage).
3. Our work described in the manuscript was partially supported by a Grant-in-Aid for Scientific Research (C) (17K10460) and we provided the certificate of funding. If it is not enough document, please delete the part of "supported by ….".
4. We checked the references and found that there were no repeated references.
5. We provided the decomposable figure of Figures with power point format (.ppt).