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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 21118
Title: Is metastatic pancreatic cancer an untargetable malignancy?
Reviewer's code: 02394722
Reviewer's country: United States
Science editor: Fang-Fang Ji
Date sent for review: 2015-07-02 09:01
Date reviewed: 2015-08-08 02:55

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In the manuscript of Marwan Ghosn et all a very important question is raised whether metastatic pancreatic cancer is an untargetable malignancy. Authors claimed that their aims are to present the major causes rendering metastatic pancreatic cancer (MPC) an untargetable malignancy and to focus on the new therapeutic modalities based on targeted therapies in MPC. Although this is a well written review, it seems that they only partially achieved their goals. In the current form manuscript presents a list of multiple approaches used to treat MPC without critical analyses of reasons of failure and potential mechanisms associated with this tough situation. I believe that the manuscript will benefit from certain restructuring and attempt to give answers on the additional questions.

First authors should include with a short overview of known molecular mechanisms of PC, since without this analyses of targeted therapies lack necessary foundation. Reasons of difficulties to treat MPC are given scarcely and mostly at the end, while in this review it should be a focused area and needs to be given in more details as a separate section. Situation with the treatment of PMC should be reviewed vis-à-vis other similar types of cancer to better understand what is so unique (if any) in MPC.

Questions which a reader has reading this review are:

- All mentioned targeted therapies were tested according to authors in combination with gemcitabine. Whether any attempts to use TT alone were made?
- What was the rationale of using mentioned TT, whether any pharmacodynamic markers were assessed? This is important to understand why these therapies failed.

Minor remarks:

- Bortezomib is not epigenetic drug
- CDKNA, TP53 and SMAD4 have many more important ways of regulation than miRNAs.
- In many instances authors mention ongoing trials without giving results or references to the trial, which is kind of useless without that.

Concluding remarks including author's opinion where to go would be interesting to include.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 21118
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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COMMENTS TO AUTHORS

This is a cursory review of the current advances in treatment for pancreatic cancer, a particularly aggressive cancer with few viable treatment options. The review covers many of the main clinical discoveries spanning the last decades; however, most of the review could benefit greatly from an increased attention to detail and expanded explanation of the covered topics. The paragraph on FOLFIRINOX should make note of the significance and type of side effects, and that the treatment is really only viable in a certain patient population (stage IV). Similarly, the GEM-elotinib paragraph needs to mention that the effect is modest and is really only beneficial to the subgroup of patients that develops a rash. In particular, the section on miRNAs could be expanded to include, not only more detail about the miRNAs involved, but also specific citations about the contribution of miRNAs to radioresistance, in particular, through mechanisms related to Beclin-1. The authors mention that CDK2NA, TP53, and SMAD4 are regulated by miRNAs, but no pathways are mentioned. Furthermore, the following paragraph concerning BRCA1 and BRCA2 would benefit from more detail about the "many ongoing trials" which are "studying this treatment options", in particular, citations of papers or ongoing trials. Anti-PARP drugs should be better defined, and the logic

between moving a breast cancer drug into pancreatic cancer could be explained more clearly. What does Hyaluronidase target? It's being used to modulate the extracellular matrix in conjunction with gemcitabine, but by what mechanism do the authors of the papers cited believe this drug to work? The genetics discussion could also include a paragraph about chromosomal instability (CIN) which is implicated in several pancreatic cell lines. Overall, the review could be strengthened by citing additional literature beyond the clinical trials and data that is shown here. By enumerating the twelve signaling pathways that the authors mention in the introduction and the discussion, they could open up the review to discuss ongoing research that examines, for example, the programmed cell death pathway, oxidative stress, chronic inflammation, and the role of TLRs in cell proliferation and chemoresistance in PC: all topics which are of ongoing research in the field. The biggest change that needs to made, is some mention and discussion of the fact that PC is so deadly due to the lack of early detection. In addition to targeted therapies being investigated, it would be good to discuss new diagnostic techniques for early detection, potential biomarkers, etc. The discussion needs to be expanded with some more significant conclusions about the state of PC, perhaps to emphasize the importance of ongoing clinical trials, the use of biomarkers to indicate the best treatment regiment, and ways to increase early detection.