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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80875

Title: Recent Advances in Targeted Therapy for Pancreatic Adenocarcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03018526
Position: Peer Reviewer
Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2022-10-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-15 17:39

Reviewer performed review: 2022-10-24 11:39

Review time: 8 Days and 18 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have carried out an extensive review of the literature taking into account numerous biological aspects of Pancreatic Cancer. They summarise current targeted therapies and clinical trials targeting dysregulated signaling pathways and components of the PDAC oncogenic process, analyse possible reasons for the lack of positive results in clinical trials and ways to improve them, and also discuss emerging trends in targeted therapies as the most promising approach. The Manuscript is written correctly and the Literature Analysis appears vast and clearly illustrated. The subject is very topical given the poor disease prognosis and the increasing in incidence.

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Reviewer's code: 03874412
Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

Manuscript submission date: 2022-10-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-18 09:35

Reviewer performed review: 2022-10-24 12:46

Review time: 6 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

This work constitutes a very interesting review in an otherwise quickly evolving scenario. Consider general English revision, grammar and style Title A reformulation of the title as "Recent advances in Targeted Therapy for Pancreatic Adenocarcinoma" is more accurate. Abstract It describes the landscape of PDAC, including the most characteristic genetic alterations, but refers to "tumor microenvironment, chemoresistant cancer stem cells, and the desmoplastic stroma" merely as targets for therapy, not as constitutive and very relevant elements of PDAC, the true reason of its relevancy as targets. To be corrected. In the final lines, "analyze possible reasons for the lack of positive results in clinical trials and ways to improve them" could be substituted by "analyze possible reasons for the lack of positive results in clinical trials and suggest ways to improve them." The sentence "also discuss emerging trends in targeted therapies as the most promising approach." has to be reformulated. The emerging trends by themselves, without any other reason, do not constitute a promising approach. As the authors properly remark in the summary "This suggests to us that, in fact, most clinical trials have also demonstrated that monotherapy of targeted drugs is not feasible. Therefore, combining targeted inhibitors of multiple pathways may be the future targeted therapy research's primary direction." This idea has to be incorporated in the abstract, as reflects the current paradigm in the development of effective PDAC's treatment strategies. Keywords Targeted therapy and Cancer stem cell are MeSH terms. Pancreatic adenocarcinoma is not a MeSH term, can be replaced by pancreatic carcinoma. Stroma targets is not a MeSH term, is poorly descriptive and does not add to "targeted therapy" whereby could be omitted. Tyrosine kinase inhibitors, again not MeSH term, could be omitted, because are not the only class

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of agents to be used as targeted therapy. As described in the text there are monoclonal antibodies, epigenetic modifiers… Core Tip Please consider the observations formulated for "Abstract" Introduction In this section, there is not a general description of the structural and biological characteristics of PDAC, essential to understand the lack of response to the common treatments, the bad prognosis and the reason for exploring the subsequently reported therapeutic strategies. Also is essential to consider this before to state, "The development of novel and effective therapeutic strategies is therefore vital to improving treatments that are both targeted and personalized.", because the necessity of targeted and personalized treatments is derived from the complexity and particularities of PDAC's structure and biology. In order to improve the above mentioned, some of the paragraphs used in other sections could be transferred here, as 4. Stroma targets or the first and third paragraphs from Summary. Material and methods No mention of any method. To be corrected. At least the time interval, keywords and database/s consulted have to be referred. Results In this type of review, there is no place for Results as such, but for a structured exposition of the findings in literature. As general observation and to be corrected, several of the acronyms used are not adequately explained in their first mention (PanIN, page 3;gBRCAm, page 9;HA, page 12;GA, page 13;MMB, page 15;nab-P+G, page 15;A2AR, page 16). The authors employed "PSC" referred to two different subjects: page 11, section 4., for pancreatic stellate cells and page 14, section 5., for pancreatic cancer stem cells. Confusing and to be corrected. In page 6, paragraphs 3rd and 4th, there is no indication about the mutational status of EGFR and KRAS in the referred studies, key for evaluating the context of efficacy of the treatments exposed. Consider the same in the 6th, referred to trastuzumab and HER2 expression or afatinib and EGFR mutations. In page 9, section 3.5, 4th line, "15 stable responses" are mentioned. Although in determinate contexts stabilizations are considered and described as a component of the global clinical

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benefit, the concept “stable responses” is not correct and has to be changed for “stabilizations”, “patients with stable disease” or similar. Summary Is correct, but lack one of the most relevant aspects indirectly exposed in the work. PDAC is a very complex entity, joining different molecular particularities and in a dynamic manner, not in a static one. As some guidelines already stated and can be concluded from de data shown here, is very important to spread the genetic and transcriptomic profiling of every PDAC in order to capture the vulnerabilities of the tumor as far as possible as the way to improve therapeutic results