



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 64701

Title: Biomarkers for Response to Immune Checkpoint Inhibitors in Gastrointestinal Cancers

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05128184

Position: Peer Reviewer

Academic degree: MD

Professional title: Academic Fellow, Research Assistant, Staff Physician

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-02-22

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-23 22:25

Reviewer performed review: 2021-07-23 22:44

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

This is a mini-review about general considerations about biomarkers for ICI in gastrointestinal malignancies (considering together a group of diseases that perhaps has many intrinsic differences in terms of biology. The main topics are covered (TMB, MSI status, PDL1, tumor microenvironment and TILs role. Relating to TMB I suggest to cite the study by Marabelle et al (Lancet Oncol, 2020, a subgroup analysis of Keynote 158 trial, doi 10.1016/S1470-2045(20)30445-9, of which there is no mention in the text). The remaining topics are well covered, however I suggest to add a specific section about single cell analysis of tumor microenvironment as a powerful tool to identify new possible biomarkers of response to immunotherapy in a large amount of tumors (only to cite one, the study by Steele et al, Nature Cancer 2021, with a complex and integrated analysis with CYTOF and scRNAseq identified TIGIT as possible target in exhausted T cells within pancreatic cancer microenvironment. But today there are more and more examples of multi-omics single cell analysis to identify possible new mechanisms of immunotherapy responses, in different GI tumors. I think that this should be addressed by the authors in more detail, considering that this technology will be the future of cancer translational research).



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Peer-review model: Single blind

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: China

Manuscript submission date: 2021-02-22

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-21 13:11

Reviewer performed review: 2021-07-24 10:45

Review time: 2 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

Generally, this review incorporates most important Immune Checkpoint Inhibitors in gastrointestinal malignancies. Please see below my comments: A. Even though based on some recent references, the authors did not incorporate other markers, that were published in previous excellent reviews on this topic or in recent studies. These reviews are much better than this one, regarding structure and organization of the material. Just some examples are listed below (for which, I have just the scientific interest in mentioning, as I am not the author and I have no personal relationship with their authors). 1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* 11, 3801 (2020). 2. Darvin P, et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med* 50, 1-11 (2018). 3. Shah, et al. Immune checkpoint inhibitors in gastrointestinal malignancies: what can we learn from experience with other tumors? *Transl Gastroenterol Hepatol* 2019;4:73 4. Kourie HR, et al. Checkpoint inhibitors in gastrointestinal cancers: Expectations and reality. *WJG* 2017 5. Güthle M, et al. Immunotherapy in Gastrointestinal Cancers. *Visc Med.* 2020 Jun;36(3):231-237. 6. Mazloom A, et al. Role of Immune Checkpoint Inhibitors in Gastrointestinal Malignancies. *J Clin Med.* 2020 Aug 6;9(8):2533. 7. Turkes F, et al. Targeting the immune milieu in gastrointestinal cancers. *J Gastroenterol* 55, 909-926 (2020). B. Also, another good paper to be mentioned would be "Lu Z, et al. Prediction of immune checkpoint inhibition with immune oncology-related gene expression in gastrointestinal cancer using a machine learning classifier. *Journal for ImmunoTherapy of Cancer* 2020;8:e000631.". C. Moreover, even though the manuscript is structured, most data are inserted in the main text, instead of being synthesized in tables (much



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easier to be followed). The only one table is too scarce. I would suggest data to be nicely structured in tables, instead of plain text. D. Many references are not updated (i.e. ref 19 mentions: Published online 2019. However, it has full published data: 2019; 37(15_suppl):4021-4021). Please update data on references. E. Also, in order to bring something new and up-to-date, ongoing trials using ICI in gastrointestinal malignancies should be inserted in a table (<https://clinicaltrials.gov>). F. Core Tip is missing from the manuscript. I read it in the Submission form. It should be inserted in the manuscript. G. Format of the style requested by the journal, including references, is not adequate. Please correct. H. There is no "Author contribution" section. Please add. ORCID number should also be added. I. There are no « Conflict-of-Interest Disclosure Form » and « Copyright License Agreement ». Please add. J. Revision of the English language is required (grammar, syntax and overall style).



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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05272326

Position: Peer Reviewer

Academic degree: MD

Professional title: Research Associate

Reviewer's Country/Territory: Albania

Author's Country/Territory: China

Manuscript submission date: 2021-02-22

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-22 16:25

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Review time: 4 Days and 23 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

This is an original and very inspiring study regarding the biomarkers for immune checkpoint inhibitors response to gastrointestinal cancers. Even though it is in an experimental phase, the data shows highly suggesting results for this kind of therapy. Comparing it to most of the East European countries it is an innovative approach to gastrointestinal cancers. The importance of this study is by showing the possibility to a personalized immunotherapy for GI cancers. Especially among these markers, the PD-L1 expression, has shown to be responsive to ICI in PD-L1-negative patients. Even though from these studies, PD-L1 as an independent biomarker, remains controversial. This study is very instructive according the necessity of the biomarkers in relation to ICIs, as an important topic in the immunotherapy of gastrointestinal cancers. The limitations of the study is that lacks validations in several clinical trials.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Peer-review model: Single blind

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: China

Manuscript submission date: 2021-02-22

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2021-10-15 13:36

Reviewer performed review: 2021-10-16 09:54

Review time: 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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

SPECIFIC COMMENTS TO AUTHORS

The authors worked hard to improve their manuscript, according to the reviewers' suggestions. I am pleased with they way it appears now. Tidy and professional, as well as up-to-date. Just a few minor corrections should be performed (mentioned in the attached file). Other than that, I noticed that Denis Kaili did not sign the Copyright License Agreement.