

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 78536

Title: Immune Checkpoint Inhibitor-Mediated Colitis Is Associated with Cancer Overall Survival

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05575380

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2022-07-02

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-03 18:31

Reviewer performed review: 2022-07-04 05:25

Review time: 10 Hours

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 Grade E: Do not publish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 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="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Despite ICI seem to have found their role in a plethora of hematological and solid malignancies, several questions remain unanswered. Among these, the lack of validated biomarkers of response represents an important issue since only a proportion of patients benefit from immunotherapy. Based on these premises, a greater understanding of the role of potential biomarkers including programmed death ligand 1 (PD-L1) expression, tumor mutational burden (TMB), microsatellite instability (MSI) status, gut microbiota and several others is fundamental. In addition, clinical trials on immunotherapy widely differed in terms of drugs, patients, designs, terms of study phases, and inconsistent clinical outcomes. Among predictors of response, also treatment-related adverse events should be considered, since a large number of reports has tried to assess this association. Based on these premises, the study assesses a current, timely topic. We recommend some changes: - We believe this article is suitable for publication in the journal although major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. Certainly, the study is limited to a single-center experience with a very small sample size, and authors should further express this point. - Second, the study included a widely varied patient population from a single institution and the total number of patients analyzed was small. Thus, the authors should better highlight the limitations of the current paper. - The background of the role of predictors of response to ICIs should be better discussed, and some recent papers regarding this topic should be included (PMID: 34429006; PMID: 34894318; PMID: 33714725). - Currently, the effect of immune-related adverse events (IrAEs) on survival of patients affected by advanced malignancies is

uncertain. A plethora of recent retrospective studies have hypothesized that the development of IrAEs in cancer patients may correlate with durable response and survival benefit, although contradictory reports exist. Despite providing interesting data, several studies investigating this association should be interpreted with caution because of an inappropriate methodology. In particular, only a minority of these reports considered the effect of immortal time bias (ITB), a key element in determining the effective association between clinical outcomes and a time-dependent variable. Of note, ITB represents a key element regarding these kind of studies since patients who die or whose disease progresses earlier are less likely to develop toxicity; in fact, these patients probably have not stayed in the study long enough to develop adverse events, or because they discontinued treatment or died due to progressive disease. Conversely, included patients that stayed in the study for a longer time interval have an increased risk to experience toxicities. The authors should consider this point and discuss it, since it may represent a very important bias in this study. Major changes are necessary.

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Title: Immune Checkpoint Inhibitor-Mediated Colitis Is Associated with Cancer Overall Survival

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05345134

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2022-07-02

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-05 03:14

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Review time: 5 Hours

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 checked="" 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

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

SPECIFIC COMMENTS TO AUTHORS

The article analyzes the literature factors of IMC in patients with malignant tumors after using ICI and its impact on PFS and OS, which has strong clinical guiding value. However, the number of cases included in the article is small, the statistical method needs to be refined, and the reliability of the results will be greatly reduced. It is suggested to expand the sample size.

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Manuscript NO: 78536

Title: Immune Checkpoint Inhibitor-Mediated Colitis Is Associated with Cancer Overall Survival

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05130847

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2022-07-02

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-05 06:55

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Review time: 9 Days and 3 Hours

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

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

The topic of this article is very interesting. The following issues deserve further discussion: 1、The results showed that IMC was significantly associated with a higher OS, Whether this association effect is different between cancer types? For example, how does the occurrence of IMC affect the OS of melanoma? 2、In addition to IMC, what is the incidence of other irAEs in the two groups of patients, and does it affect cancer prognosis?

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

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Peer-review model: Single blind

Reviewer's code: 05575380

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2022-07-02

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2022-09-26 11:53

Reviewer performed review: 2022-09-26 11:55

Review time: 1 Hour

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



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statements

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

SPECIFIC COMMENTS TO AUTHORS

The authors addressed all the queries and issues we raised. We recommend Acceptance.