

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 39616

**Title:** PROGNOSTIC SIGNIFICANCE OF TUMOR IMMUNE MICROENVIRONMENT AND IMMUNOTHERAPY: NOVEL INSIGHTS AND FUTURE PERSPECTIVES IN GASTRIC CANCER

**Reviewer's code:** 03270412

**Reviewer's country:** Turkey

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2018-05-07

**Date reviewed:** 2018-05-07

**Review time:** 0 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

MSI-High is pathological immunostaining definition. The Author(s) should define clearly What is the discordance MSI-H pathologically report and genetically somatic mutated



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MSI .Is there any relation with tumor mutational burden.

#### INITIAL REVIEW OF THE MANUSCRIPT

##### *Google Search:*

- ☐ The same title
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- ☐ Plagiarism
- ☐ No

##### *BPG Search:*

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**Reviewer's code:** 03551828

**Reviewer's country:** Japan

**Science editor:** Ze-Mao Gong

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
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			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

I am sending herewith my comments regarding the manuscript entitled "PROGNOSTIC SIGNIFICANCE OF TUMOR IMMUNE MICROENVIRONMENT AND

IMMUNOTHERAPY: NOVEL INSIGHTS AND FUTURE PERSPECTIVES IN GASTRIC CANCER.” In this manuscript, authors reviewed the mechanism of tumor immune microenvironment and the immunotherapeutic strategies including immune checkpoints inhibitors for gastric cancer. I would like to point out several issues. Major points; 1) In line 29 of page28, you described that the response rates for patients with PD-L1+ tumors (>1% of immunohistochemically positive cells), both in patients treated with nivolumab monotherapy and combined treatment nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, were superior compared to patients with negative tumors (27% vs. 12% and 44% vs. 21%, respectively). However, I think that the response rates for patients with PD-L1+ tumors in patients treated with combined treatment nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3+I1) were superior compared to patients with negative tumors (27% vs. 0%). The authors should add the result of combined treatment N3+I1. 2) In line 3-9 of page29, they mentioned that checkmate-649 has planned to investigate 1349 patients with naive advanced or metastatic gastric/gastroesophageal junction (GEJ) cancer with both positive/negative PD-L1 expression to receive first line nivolumab plus ipilimumab vs. standard chemotherapy (XELOX or FOLFOX). However, checkmate-649 have nivolumab plus standard chemotherapy (XELOX or FOLFOX) arm as experimental arm. They should describe the nivolumab plus standard chemotherapy arm. 3) In line 10 of page29, the ATTRACTION-2 trial has already reported the association between PD-L1 expression and prognosis. The authors should add the efficacy by PD-L1 expression status. 4) In line 27 of page30, they mentioned the data from the KEYNOTE-059 trial at the ASCO congress. However, a phase 2 clinical KEYNOTE-059 trial has been published on JAMA Oncology in 2018. ORR was a little different (11.6%). They need to make changes along the literature. 5) In line 27 of page31, the results of KEYNOTE061 have already been published as a press release on web. They should add the efficacy from the KEYNOTE-061. 6) In line 25 of page32, the results of the JAVELIN Gastric 300 trial have

already been published as a press release on web. They should add the efficacy of the JAVELIN Gastric 300 trial. 7) In line 28-31 of page32, they mentioned the results of JAVELIN program which reported at ASCO meeting 2016. What is first context and second setting? Perhaps, I think that first context and second setting mean first line maintenance and second line, respectively. They should add the detail results. 8) The clinical trial of nivolumab with paclitaxel and ramucirumab in patients with advanced, unresectable gastric cancers is ongoing under investigation in a phase I/II study (UMIN000025947). The authors should add the clinical trial in future perspectives contexts. Minor points; 1) The authors should mention 'Ib' rather than '1b or 1B'. 2) They should mention 'gastric' rather than 'stomach'. 3) Page12, line4. Two thirds add '-' (hyphen)' between two and thirds. 4) Page15, line18. In line 15 of page 15, the abbreviation of cytokine-induced killer has already been described. 'cytokine-induced killer' might want to be omitted. 5) Page16, line8. In line 5 of page 16, the abbreviation of epidermal growth factor receptor has already been described. 'epidermal growth factor receptor' might want to be omitted. 6) Page16, line23.29 'stage II-III' and 'stageIII/IV' have the mixture of hyphen and slash. 7) Page17, line4. In line 5 of page 16, the abbreviation of cytokine-induced killer has already been described. 'cytokine-induced killer' might want to be omitted. 8) Page17, line30. What is the definition of HER2 positive? 9) Page18, line24. What is 'gastric Th17 response'? You should add the meaning about Th17. 10) Page20, line26. Is 'HSPs' better than 'HPS'? 11) Page17, line4. In line 5 of page 16, the abbreviation of cytokine-induced killer has already been described. 'cytokine-induced killer' might want to be omitted. 12) Page22, line8. In line 16 of page 20, the abbreviation of vascular epidermal growth factor receptor has already been indicated. 'Vascular epidermal growth factor' might want to be omitted. 13) Page23, line22. PD-L1 expression level should be indicated. 14) Page24, line25. Literature number '2012' is wrong. Is 202 correct? 15) Page25, line10. 'stage II-III' might want to be slash.



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16) Page25, line22. 'GCs' should be gastric cancers. 17) Page27, line13. The abbreviation of overall survival has already been described. In line 13 of page27, 'overall survival' might want to be omitted. 18) Page29, line28. The abbreviation of the programmed cell death 1 has already been described. 'the programmed cell death 1' might want to be omitted. 19) Page33, line27. What is 'resected lower'? You should add the meaning about 'resected lower'. 20) Page34, line8. 'stage II-III' might want to be hyphen. 21) Page35, line9. 'Her-2' might want to be changed 'HER2'. 22) Page36, line7. What is 'MELK'? The authors should add the meaning about MELK. 23) Page37, line11. 'GC' may be 'gastric cancer'.

## **INITIAL REVIEW OF THE MANUSCRIPT**

### ***Google Search:***

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- ☐ Duplicate publication
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**Reviewer's code:** 01804931

**Reviewer's country:** China

**Science editor:** Ze-Mao Gong

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**Review time:** 7 Days

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			Conflicts-of-Interest:
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## SPECIFIC COMMENTS TO AUTHORS

This is a very comprehensive review of the immuno microenviroement and developing immunotherapy of gastric cancer. The manuscript is well written and the data review





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is adequate. However, it is difficult for the reader to understand. Most of the trials shown in Table 1 are inconclusive and not very helpful. The author should try to make a figure to show the microenvironment of gastric cancer and to explain the current consensus to help our reader to understand the update knowledge. An algorithm of current treatment is also helpful for our reader to understand.

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