



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45008

Title: Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond

Reviewer's code: 00006459

Reviewer's country: Australia

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-18

Date reviewed: 2018-12-22

Review time: 5 Hours, 4 Days

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

This is an excellent review for clinicians and others who wish to be up to date concerning recent and potential near future new medicines for HCC. The information is current and so is best published quite soon. Many useful details are included for the



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clinician. Mechanism of action of each medicine is not a focus and does not need further content for this review to be excellent. Many useful comments are made by the author. For example, moving towards using lenvatinib as first-line. The author comment about weight-based dosing is commended; I encourage addition of any further evidence that can be cited that would support this conclusion. There are competing interests declared. My comments for manuscript improvements are: 1. It is necessary to add information and commentary about adverse events / side effects that were associated with the new medicines. 2. Please add reference numbers to each table so that there is clarity regarding the publication or publications that the presented data is derived from. 3. I prefer that in each figure legend there be clarity regarding the publication or publications that the data referred to is derived from. 4. The paragraph that extends over pages 17 and 18 could be reconsidered to provide greater clarity, please. I would not use the word "extremely" here. 5. Page 18 para 2: rephrase "This will increase .." 6. Page 20: I suggest even more caution in comments on data that, as is mentioned, is from n=21 and n=26 patients.

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45008

Title: Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond

Reviewer's code: 00503516

Reviewer's country: Italy

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-11

Date reviewed: 2018-12-23

Review time: 14 Hours, 12 Days

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 polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Masatoshi Kudo describes the most recent novelties in the field of HCC treatment also proposing possible future development. The paper is very well written and contains informative notions with regard to the practical use of the novel drugs developed. I



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suggest to better explain the sentence reported on page 5:” Although eight clinical trials conducted in the last decade has shown negative outcomes, the results of the REFLECT trial met its primary endpoint”. It seems that Lenvatinib has been tested in eight clinical trials before REFLECT with negative results: is this the meaning of the sentence? By looking at table 1, it does not seem that Lenvatinib has been used in clinical trials 1-8. It is necessary to more extensively describe the data reported in figure 4. In figure 5, it is necessary to specify the time measure unit (weeks? Months?)

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45008

Title: Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond

Reviewer’s code: 03538879

Reviewer’s country: China

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-18

Date reviewed: 2018-12-24

Review time: 18 Hours, 5 Days

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 checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" 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 checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript summarizes the current development of targeted therapy and immunotherapy for Hepatocellular Carcinoma, the summary was very comprehensive and detailed, and the future treatment strategies were prospected. I suggest that this



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manuscript be published after answering the following questions. 1. The enhanced efficacy of combination therapies rely on the identification of serum or tissue biomarkers that would allow a better patient selection for individual treatments. So, can you comment on that about the biomarker identification for HCC treatments? As we know, with the best suitable biomarkers we selected may decide the patients who are fit for one or combination therapy. 2. What's your opinion on the ongoing CheckMate-459, Everyone is eagerly awaiting the results. Is it will be a huge change if the results are positive?

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45008

Title: Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond

Reviewer's code: 00069630

Reviewer's country: China

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-18

Date reviewed: 2018-12-24

Review time: 20 Hours, 5 Days

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
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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

Systemic therapy for hepatocellular carcinoma has markedly advanced since the survival benefit of a molecular targeted agent, sorafenib. In the past 2 year, this field has developed so rapidly with some successful clinical trials. In this review, the author



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summarizes several important clinical trials of molecular targeted agent on hepatocellular carcinoma in recent years. On this basis, the authors further summarized the data and current status of sequential application of these targeted drugs, as well as the progress in combination with TACE and immunological checkpoint therapy. These novel drugs and treatment strategies are very promising. Some ongoing clinical trials and results are eagerly awaited. We can imagine, patients with HCC will benefit more from the advance of systemic therapy in the near future. It should be said that this is an excellent summary. It provides a full and profound understand on hepatocellular carcinoma systemic therapy for clinical physician. I recommend that this review be published as soon as possible.

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