



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer’s code: 03724099

Reviewer’s country: United States

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-08 02:45

Reviewer performed review: 2019-04-08 02:58

Review time: 1 Hour

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

SPECIFIC COMMENTS TO AUTHORS

Very well written, detailed review. Few typo-graphical erros such as Page 3 line 2 - change approx. to approximately Page 3 second last line - change closer to closely.



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INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer's code: 03475479

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-08 03:01

Reviewer performed review: 2019-04-09 05:46

Review time: 1 Day and 2 Hours

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 checked="" 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 type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" 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

Author reviewed recent advances in the treatment and biomarkers of HCC. This review is well-written and well-summarized, and can provide readers up-to-date knowledge about HCC.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer’s code: 00058381

Reviewer’s country: Austria

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-09 09:02

Reviewer performed review: 2019-04-09 16:55

Review time: 7 Hours

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 polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" 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

This manuscript offers an overview on hepatocellular carcinoma in research and clinical practice; however, the outlook provided at the end of the text is very general; both from the scientific and clinical point of view, more specific statements (e.g., on the most



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promising therapeutic options in the near future) would be desirable. Additional Comment: Language polishing is necessary; e.g., "with similar toxicity than regorafenib" (p.4); "lacking HCC formation for high-fat diety" (p.12); "Furthermore, the biological roles the identified driver genes in HCC must be analyzed in the deeper integration of inter- and intratumoral, interpatient, and inter-ethnic tumor heterogeneity in more detail" (Conclusions and Outlook).

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer's code: 02904354

Reviewer's country: China

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-08 01:17

Reviewer performed review: 2019-04-13 10:25

Review time: 5 Days and 9 Hours

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 checked="" 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 checked="" 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 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

Overall, this paper is well written. I recommended the revision. Based on my personal experiences, some comments are provided as follows. 1. The current title "Hepatocellular carcinoma in research and clinical practice" is too broad and



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comprehensive; by comparison, the main text focused on the new tyrosine kinase inhibitors, epigenetic modifiers and increasingly also cell therapy and immune checkpoint inhibitors. Indeed, the advance in the management of HCC has been also seen in the field of surgery, radiation therapy, and ablation. Therefore, the title should be revised. Otherwise, the introduction should be expanded by adding some new information and recent evidence (PMID: 30799321; PMID: 27167195). 2. The organization of this paper should be further improved. 3. Are you sure that smoking is a major risk factor of HCC? Please improve the words. 4. Met inhibitors for HCC, as previously reviewed in a paper in this journal (PMID: 25987766), should be reviewed in the paragraph regarding "Conventional chemotherapy and molecular targeted therapies". 5. Despite the use of sorafenib for advanced HCC has been proved, its role in HCC with PVTT remained questioned (PMID: 26516379). 6. Full names with their corresponding abbreviations at the first time of occurrence, such as OS, HCC, and RFS, should be carefully checked and revised. 7. Some spelling errors, such as "diety", are observed. A native English speaker should be employed to revise this paper. 8. Grammar "...still remain..." may be questioned.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer’s code: 00182114

Reviewer’s country: Japan

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-13 07:52

Reviewer performed review: 2019-04-14 05:24

Review time: 21 Hours

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 type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" 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

This is very interesting paper. Author reviewed that novel therapeutic approaches and different preclinical model for HCC drug discovery and development for advanced HCC. 1.It is possible that not only Child-Pugh score 5 and 6 but also 7 patients are



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eligible for future clinical trials with sorafenib or similar drugs. The median overall survival of Child-Pugh score 5, 6, 7 and ≥ 8 patients were 14.5, 11.1, 8.7 and 4.6 months, respectively. Patients in Child-Pugh score 6 had significantly longer OS than those in Child-Pugh score 7 ($P = 0.049$). (Sorafenib treatment in Child-Pugh A and B patients with advanced hepatocellular carcinoma: safety, efficacy and prognostic factors. Invest New Drugs. 2015 Jun;33(3):729-39.) Author writes all of these compounds are recommended for patients with preserved liver function ,ie child-Pugh A or low B. Score of Child A is 5-6. Score of Child B is 7-9. But Score of Child (7,8) is prognosis poor according to above paper. Therefore, I think author should revise Child-Pugh score 5,6 and 7. 2. Some researchers have suggested that vitamin K enhances the antitumor effect of sorafenib for hepatocellular carcinoma (HCC) in vitro and in vivo. In this study, Haruna et al examined the clinical impact of vitamin K dosing for sorafenib treatment. This is the first clinical report showing enhanced antitumor action of sorafenib by vitamin K. Haruna's clinical findings suggest that vitamin K may have the synergistic effect by suppressing production of DCP, a tumor growth and angiogenesis factor. (Clinical Impact of Vitamin K Dosing on Sorafenib Treatment for Hepatocellular Carcinoma J Cancer 2017; 8(11):1988-1994.) Please write vitamin K enhance the antitumor effect of sorafenib for HCC in this paper. 3. CD44v9 could be a novel biomarker of liver TISCs and a prognostic factor for HCV+ HCC patients. CD44 variant 9 is a potential biomarker of tumor initiating cells predicting survival outcome in hepatitis C virus-positive patients with resected hepatocellular carcinoma. Cancer Sci. 2016 May; 107(5): 609-618 Please write the detail mechanism of biomarker of CD44v9 and HPCAL1 for HCC.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer’s code: 02529007

Reviewer’s country: Iran

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-08 17:36

Reviewer performed review: 2019-04-15 12:34

Review time: 6 Days and 18 Hours

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 polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" 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 type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input checked="" 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

Manuscript # 48028 entitled, “Hepatocellular carcinoma in research and clinical practice” is an attempt to make a review article on conventional therapies on HCC and those in clinical trials such as: novel immunotherapy targets, epigenetic therapy (HDACi) and



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cell therapy (CAR-T cells) approaches. In addition, considering that the development of novel drugs might require further advanced pre/sub clinical knowledge, the manuscript provides two further sections entitled, “Novel biomarkers to improve patient outcome” and “new preclinical models to improve HCC therapy”. Finally, it is concluded that, each HCC specimen might be analyzed and treated on an individualized/personalized basis, while advanced tumor models are needed to close the gap between in vitro experiments and clinical trials and advanced technologies might be required to interpret the obtained OMIC/imaging data on HCC. Comments: There are increasing number of “review articles” published on different aspects of HCC in last few years. Indeed, just since 2018 to date (April 2019) more than 1000 “review articles” on detailed/separate aspects of HCC is published in a number of different journals including “WJG”. In fact, all the entitled sections of the present review article are introduced as single/individual and separate review articles, focused on a specific aspect of the subject, rather than a combination of several subjects. Of note, they represent almost the same information in the summarizing tables as modified in the present manuscript. For example, in the following, few recently published related “review articles” in 2019/2018 might be mentioned. Of note, none of them are quoted in the present manuscript. • Regarding regular and immune/epigenetic therapies on HCC: - Chang Lee R, Tebbutt N. Systemic treatment of advanced hepatocellular cancer: new hope on the horizon. *Expert Rev Anticancer Ther.* 2019 Apr;19(4):343-353. - Kudo M. Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond. *World J Gastroenterol.* 2019 Feb 21;25(7):789-807 - Sun JY, Yin T, Zhang XY, Lu XJ. Therapeutic advances for patients with intermediate hepatocellular carcinoma. *J Cell Physiol.* 2019 Jan 15. - Tsilimigras DI, Ntanas-Stathopoulos I, Moris D, Spartalis E, Pawlik TM. Histone deacetylase inhibitors in hepatocellular carcinoma: A therapeutic perspective. *Surg Oncol.* 2018 Dec;27(4):611-618. • Regarding role of Biomarkers on HCC: - Harding JJ, Khalil DN,



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Abou-Alfa GK. Biomarkers: What Role Do They Play (If Any) for Diagnosis, Prognosis and Tumor Response Prediction for Hepatocellular Carcinoma? *Dig Dis Sci.* 2019 Apr;64(4):918-927. - Tapper EB, Loomba R. Noninvasive imaging biomarker assessment of liver fibrosis by elastography in NAFLD. *Nat Rev Gastroenterol Hepatol.* 2018 May;15(5):274-282. • Regarding regular preclinical and animal models on HCC: - Ippolito D, Pecorelli A, Querques G, Drago SG, Maino C, Franzesi CT, Hatzidakis A, Sironi S. Dynamic Computed Tomography Perfusion Imaging: Complementary Diagnostic Tool in Hepatocellular Carcinoma Assessment From Diagnosis to Treatment Follow-up. *Acad Radiol.* 2019 Mar 6. pii: S1076-6332(19)30076-5. - Jiang M, Wu N, Chen X, Wang W, Chu Y, Liu H, Li W, Chen D, Li X, Xu B. Pathogenesis of and major animal models used for nonalcoholic fatty liver disease. *J Int Med Res.* 2019 Apr;47(4):1453-1466. - Zhang Z, Song L, Guo J. The Application of Pre-clinical Animal Models to Optimise Nanoparticulate Drug Delivery for Hepatocellular Carcinoma. *Pharm Nanotechnol.* 2018;6(4):221-231. Therefore, it seems that the novelty of the present manuscript relies on providing only a “general review/view” on several aspects of HCC (as introduced by five section-titles in the manuscript) rather than a “specialized review/view” on a specific aspect of HCC or just “emphasizing the need of advancement of preclinical research for advancement of therapies (or otherwise, the main aim and novel idea of the manuscript compared to the great # of recently published review articles on the same subject might be clearly declared by authors). If so, in my opinion, it would be better to address the idea of this manuscript by arranging a “mini review article, implying the very recent updates on these subjects” or simply “an editorial” and starting from these recent published review articles on the same sections (some examples are outlined above). In this way, a summarized and targeted manuscript (either mini-review or editorial) with minimum required references (almost all belonging to recently published review articles on these five sections) might be arranged. Of particular note, this



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approach is relatively undertaken by authors concerning "animal models" subject only. That is, they have referred to two related recently published review article to summarize their points (- Lau JKC, Zhang X, Yu J. Animal Models of Non-alcoholic Fatty Liver Diseases and Its Associated Liver Cancer. Adv Exp Med Biol. 2018;1061:139-147. -Takakura K, Oikawa T, Tomita Y, Mizuno Y, Nakano M, Saeki C, Torisu Y, Saruta M. Mouse models for investigating the underlying mechanisms of nonalcoholic steatohepatitis-derived hepatocellular carcinoma. World J Gastroenterol. 2018 May 14;24(18):1989-1994

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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- No

BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48028

Title: Hepatocellular carcinoma: Therapeutic advances in signaling, epigenetic and immune targets

Reviewer's code: 02526287

Reviewer's country: Italy

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-09 09:25

Reviewer performed review: 2019-04-15 13:50

Review time: 6 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input checked="" 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 type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" 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

We read with interest the manuscript entitled: " Hepatocellular carcinoma in research and clinical practice" By Neureiter et al. It is a very complete, exhaustive and updated review on the novel therapeutic approaches to advanced HCC which still represents an



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unmet medical need. Language and style are outstanding. No major comments on the manuscript are needed.

INITIAL REVIEW OF THE MANUSCRIPT

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- No

BPG Search:

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