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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
Ms: 2977
Title: Mechanisms of resistance to sorafenib and the strategies in hepatocellular carcinoma
Reviewer code: 02462252
Science editor: l.l.wen@wjgnet.com
Date sent for review: 2013-03-29 14:51
Date reviewed: 2013-03-29 17:15

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS

COMMENTS TO AUTHORS:
This is a good overview of drug resistance to sorafenib in hepatocellular cancer. The paper is well written, current and should be of interest to the readership of the journal.

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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
Ms: 2977
Title: Mechanisms of resistance to sorafenib and the strategies in hepatocellular carcinoma
Reviewer code: 01566206
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS

COMMENTS TO AUTHORS:
This is a good review on the resistance of sorafenib. However, as detailed below, a number of recent studies have not been taken into account, which should be corrected. Comments 1. Page 4: replace "sorafenib was shown to have a limited median time of symptomatic progress and a lower partial response rate due to drug resistance" by "sorafenib was shown to result in a limited increase in median time to symptomatic progression and a low partial response rate due to drug resistance" 2. Replace everywhere "sorefanib-resistance " by "sorafenib resistance" 3. Page 4: indicate the range of IC50 values for sorafenib in vitro 4. Replace "Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf by inhibiting the RAF/MEK/ERK signaling pathways" by "Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf, thus inhibiting the RAF/MEK/ERK signaling pathways ". The inhibition of pERK is a consequence of the effect on Raf, thus the "moreover" is not justified 5. Page 5: The correlation between pERK levels and response to sorafenib has not been confirmed. This has not been formally published but has been presented at several meetings and discussed by JM LLovet (see for instance Villanueva GASTROENTEROLOGY 2011;140:1410 – 1426) 6. Replace "appraised" by "assessed" 7. Replace "muddy" by "of uncertain value" 8. Page 6: replace "unattached" by "unscathed" 9. JAK is not inhibited but activated by the mentioned receptors 10. Page 8: replace "Emerging evidence suggests that EMT is involved in and targeting EMT…" by "Emerging evidence suggests that EMT is involved in resistance and and that targeting EMT…" 11. Replace "The above studies indicate that EMT is involved in the resistance to sorafenib in HCC" by "The above studies indicate that EMT may be involved in the resistance to sorafenib in HCC" 12.

Page 10 : the results of the phase II study of brivanib have not been confirmed in a large phase II study, the results of which having been presented in major liver and cancer meetings recently. Thus, the paragraph should be modified. 13. The chapter on tivantinib should be partly rewritten. Indeed, a major finding of this study was to show that only patients with high levels of Met prior treatment benefited from the treatment, indicating that Met could be a predictive biomarker in this case.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS

COMMENTS TO AUTHORS:
Sorafenib is one of the choices for the treatment of HCC. The authors summarized the possible mechanisms of resistance to sorafinib in HCC treatment, and the strategies for overcoming it. This will benefit the doctors in clinical works, thus it is a good topic and the current article would have an opportunity to be published. But there are still some comments as follows: 1. The title may be good as "Mechanisms and the strategies of resistance to sorafinib in hepatocellular carcinoma". 2. Please check these sentences because their meanings are not clear: /...has also drawn attention as sorafenib, as a multilkinase inhibitor, targets several ... /...The parallel PI3K/Akt pathway remains unattached, when sorafenib targets the MAPK pathway and tyrosine kinases by inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Ret and c-kit... /...Emerging evidence suggests that EMT is involved in and targeting EMT can reverse the resistance of antitumor drugs. 3. In "CONCLUSION" section, the second sentence "The primary resistance of hepatocellular carcinoma (HCC) to sorafenib..." should be "The primary resistance of HCC to sorafenib..."

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ESPS Peer-review Report
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Title: Mechanisms of resistance to sorafenib and the strategies in hepatocellular carcinoma
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
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		[ ] No records	[ ] Major revision

COMMENTS

COMMENTS TO AUTHORS:
Sorafenib is a multikinase inhibitor of Raf kinase, which is involved in cancer cell proliferation, as well as of VEGFR-2/-3 and PDGFR-β, which is involved in peritumor neovascularization. The drug has been demonstrated to significantly prolong the time-to-progression and survival time in patients with advanced HCC in a phase III placebo-controlled study; therefore, it has been established as a standard therapy for advanced HCC. However, the mechanisms of resistance to sorafenib remain to be clarified. This review article focuses on the presumed mechanisms of resistance to sorafenib and the effective strategies for overcoming sorafenib resistance. This article is well-structured and very informative. However, there are some concerns that may require the authors' attention. Major comments 1. The preclinical study findings on the mechanisms of resistance to sorafenib are well-written and up to date, whereas the results of clinical trials are not up to date. In regard to combination therapies involving sorafenib, randomized phase II trials of doxorubicin plus sorafenib vs. doxorubicin, and a phase III trial of sorafenib plus erlotinib vs. sorafenib have already been reported. As for second-line treatment, a phase III trial of brivanib versus placebo has been reported. In addition, phase III trials such as everolimus or ramucirumab, and randomized phase II trials, such as axitinib or GC33 are presently ongoing. The authors should comment on these trials. 2. No tables or figures are included in this manuscript. Tables and figures illustrating the study findings make it easier to understand the contents of a manuscript.