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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4969
Title: ALK gene copy number gain and its clinical significance in hepatocellular carcinoma
Reviewer code: 02441249
Science editor: Gou, Su-Xin
Date sent for review: 2013-08-06 21:31
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] 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 TO AUTHORS
1. The INTRODUCTION is unstructured and extends for more than 470 words. 2. Discussion of the results is too brief and should be elaborated more.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4969
Title: ALK gene copy number gain and its clinical significance in hepatocellular carcinoma
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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
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[Y] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The authors examined the status and clinical significance of ALK gene alterations in hepatocellular carcinoma (HCC) patients. They found that ALK/CNG, but not translocation of ALK, is common in HCC and is an unfavorable prognostic predictor for HCC patients. Their findings may be relevant to the clinical practice. There are several issues and questions to be addressed. Major 1. This study suggests that the ALK/CNG positivity has clinical implication in advanced HCC patients. Therefore, the gene copy number gain of ALK is the phenomenon that develops along with the progression of the tumors but not early event of the tumor. This should be clearly notes in the discussion. 2. Did the authors examine the amplification of genes other than ALK that have been reported to be of clinical importance? 3. The authors investigated the ALK gene alteration and discussed on it. However, they did not mention the gene expression of ALK. There appeared the following report. Shao CK, Su ZL, Feng ZY, Rao HL, Tang LY. Significance of ALK gene expression in neoplasms and normal tissues. (Article in Chinese) Ai Zheng. 2002 Jan;21(1):58-62. 4. The first paragraph in the discussion seems to be a review without referring the present study results. 5. The design of this study seems to be retrospective study. This should be clearly described in the manuscript. Minor 1. In the Results section, "The cancer TNM stage was defined according to the 1997 American Joint Committee on Cancer (AJCC) staging system. Cancer histopathological classification was defined according to World Health Organization classification criteria" should be moves to the Materials and Methods section. 2. The reviewer can't understand how the values derived from: "The OS rates showed a marginal statistically significant difference between the ALK/CNG positive and ALK/CNG negative HCC patients (21.4% vs. 32.4%; P = 0.089) (Figure 2A) in page 8". 3. "In addition, HCC patients with ALK/CNG had a significantly poorer prognosis than other patients (3.6%

vs. 28.5%; P = 0.048)" in the abstract. The values presented in % need more explanation, such as survival rate at 3 years. In page 9, again, the values presented should be reconsidered: "In advanced stage (stages III-IV), the 3-year OS and PFS rates for ALK/CNG positive patients were 15.4% and 10.3%, respectively, which were significantly poorer than that of the ALK/CNG negative HCC patients (0% vs. 18.8%; P = 0.054 and 0% vs. 12.5%; P = 0.007, respectively) (Figure 3A and 3B)" 4. The following sentence appeared in the abstract should be revised. "Patients with progression-free-survival in the advanced stage (stages III-IV) and overall survival in Grade III had statistically less ALK/CNG than early stage/Grade II patients (0% vs. 12.5%; P = 0.007 and 13.3% vs. 28.9%; P = 0.023, respectively)" 5. In page 11, it is not clear what kind of failure that the authors intended to mention: "HCC has a high failure rate …". 6. In the supplementary Table 1, the values should be better presented in the order of ALK/CNG, such as ALK/CNG>6, ALK/CNG>5, ALK/CNG>4, and ALK/CNG>3.

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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
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[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

It is interesting that ALK/CNG was detected in 13.15% of HCC patients. Unfortunately there were no positive cases for ALK gene rearrangements as detected by break-apart FISH. However, ALK/CNG had a significantly worse prognostic impact on PFS of HCC patients, especially for patients with advanced stage, grade III pathologically. 4% CHD group could not take advantage, so this study could not give the impact clinically. Overall, this manuscript is highly relevant and interesting. However, there are several problems in the present manuscript so that major revision must be required before the judgement of acceptance. There are several serious criticisms as follows. 1.The PFS rates showed a statistically significant difference between ALK/CNG positive and ALK/CNG negative HCC patients. Recurrent HCC was categorized into two groups prior to the study, as intrahepatic metastasis recurrence or multicentric recurrence. Background liver affects postoperative multicentric recurrence. However, in the recurrence free survival analysis, there were no mention of background liver function, such as Child-Pugh score, platelet count and state of viral hepatitis. You should re-analysis the survival, along with these factors. 2.Why ALK gene copy number affected the survival of HCC patients, in spite of no characteristic difference such as stage, pathological grade, AFP level, and recurrence rate between 2 groups? How you presume about the mechanism of ALK gene number that affect prognosis? If ALK gene affects cancer cells proliferation, you should analyze the relation between some of tumor volume of HCC patients and ALK gene status. If ALK gene affects tumor invasiveness, you should evaluate about vascular invasion or growth patterns and ALK gene status. 3.Regarding the study design. In this study, the authors used ≥ 4 copies per cell in ≥40 of 100 cells analyzed as a cut-off for ALK/CNG positivity based on the overall consistency of survival data, because the criteria for ALK/CNG has not been established. But I think it may lack in

persuasiveness if you want to newly establish the criteria. So, you should set a cut-off value according to calculated ROC curve. If it could not do it, please state the reason not to be able. 4. In this study, the primary endpoint was overall survival (OS). However, there was no significant difference between 2 groups in OS. So, I think the final conclusion sentence is too strong and not entirely supported by this paper.. 5.You should cite a reference about "ALK belongs to the insulin receptor superfamily of tyrosine kinase receptors –", at page 11, line 12 of Discussion section.