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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 12053
Title: Prognostic value of KRAS and BRAF mutations in curatively resected colorectal cancer
Reviewer code: 00928913
Science editor: Ya-Juan Ma
Date sent for review: 2014-06-20 20:21
Date reviewed: 2014-07-05 20:57

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	[ ] Existing	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

Kadowaki et al. aimed to investigate the prognostic role of KRAS and BRAF mutations after adjustment for microsatellite instability (MSI) status in 813 Japanese patients with curatively resected, stage I to III CRC between July 1999 and May 2006. They found that KRAS mutations occurred more frequently in females than in males ($P = 0.02$), while the presence of BRAF mutations was significantly associated with the female gender ($P = 0.006$), proximal tumor location ($P < 0.001$), mucinous or poorly differentiated histology ($P < 0.001$), and MSI-high tumors ($P < 0.001$). After adjusting for relevant variables, including MSI status, KRAS mutations were associated with poorer DFS and OS. BRAF mutations were poor prognostic factors for DFS and OS. Neither the BRAF by MSI interaction test nor the KRAS by MSI interaction test yielded statistically significant results for DFS and OS. The results seems informative; however, there are a lot of criticisms and have several issues that the authors need to address before the manuscript is suitable for publication. Major Compulsory Revisions: 1. The major point that authors have to elucidate is why they analyze the prognostic roles of both KRAS and BRAF mutation status after adjustment for microsatellite instability (MSI) status. KRAS mutation is categorized to chromosome instability (CIN) pathway of CRC tumorigenesis, while BRAF mutation is categorized to MSI pathway of CRC tumorigenesis. 2. In the Materials and Methods section, there were 813 tumor samples were used for subsequent analysis. However, in Table 1, there was one missing tumor tissue in KRAS mutation analysis and two missing

tumor tissues in BRAF mutation analysis. The reason for the inconsistent data in the text and Table 1 should be proposed. Also, the incidence of MSI-H was relatively low than previous publications. 3. In Figure 1, Kaplan–Meier curves for disease-free survival (DFS) and overall survival (OS) according to KRAS or BRAF status. Presence of BRAF mutations was not significantly associated with poorer DFS and OS in the entire cohort (Figure 1; Tables 2). On the contrary, BRAF mutation status was prominently associated with DFS and OS in Cox proportional models (Table 3). Consequently, the contradictory role of BRAF mutations in DFS and OS must be elucidated and discussed in the Discussion section. 4. MSI-H tumors were only 8.2% in the current styudy, of which was considerably lower than the approximately average 10-15% than previous study. If it is possible from the PCR analysis on ISH method they used. In addition, in table 2, authors classified tumor location to proximal, distal and rectum. However, according to recent gene signature/pathway differences, now it is the trend to category CRC tumors to left vs. right colon tumors of patients. 5. MSI-H patients were demonstrated to have no advantage of receiving adjuvant chemotherapy in colon cancer patients. If the similar findings are also observed in the current study? 6. The effect of KRAS mutations on DFS and OS was limited to patients with MSS/MSI-L tumors. If the addition of adjuvant chemotherapy would play a role among these patients? 7. Despite the BRAF mutation data from Taiwan and Japan were discussed, authors just cited the studies of KRAS mutations on DFS and OS of Caucasian CRC patients, but no relevant study from Asian countries. The differences between Caucasian CRC and Asian CRC patients are suggested to be mentioned in the Discussion section. Recently, an article published from Asian country, similar to the PETACC-3 trial, their results showed that there is no significantly different between KRAS wild-type and KRAS mutation UICC stage I-III CRC patients, of which is suggested to cite it. (The Prognostic Values of EGFR Expression and KRAS Mutation in Patients with Synchronous/Metachronous Metastatic Colorectal Cancer. BMC Cancer. 2013 Dec 13;13(1):599). Thus, the discrepancy in KRAS mutations status between Western and Asian populations may be

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ESPS PEER REVIEW REPORT

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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	[ ] Existing	[ ] 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	[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The paper by Kadowaki et al. reports on a study investigating the prognostic role of KRAS and BRAF mutations in Japanese cohort of 811 colorectal cancer (CRC) patients. The topic is interesting as, to date, there are no conclusive data about the clinical utility of KRAS status assessment in the management of patients affected by CRC. The paper is well written and the population in quite large to reach useful information. The main limit of the study is the lack of any information regarding which kind of KRAS mutations have been assessed. It is well known that a large amount of literature has been published regarding the role of KRAS mutations, especially in codons 61 and 146, but also in codons 12, 13 and 117. Different mutations have been related to a different outcome of disease (see for example, only demonstrative and not exhaustive, a recent paper by Imamura et al. "Analyses of clinicopathological, molecular, and prognostic associations of KRAS codon 61 and codon 146 mutations in colorectal cancer: cohort study and literature review" in Mol Cancer 2014 May 31;13:135. doi: 10.1186/1476-4598-13-135). Authors should furnish data regarding the codons assessed for KRAS mutations, survival and disease free data have to be evaluated taking into account the codons analyzed.

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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] 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	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This is well written and illustrated paper. The authors investigate the prognostic role of KRAS and BRAF mutations after adjustment for microsatellite instability (MSI) status. And they demonstrated that KRAS and BRAF mutations are associated with inferior survival, independent of MSI status in Asian colorectal cancer population. As the authors mentioned, in contrast to previous reports, their analysis did not show that patients with MSI-H tumors exhibited better survival than those with MSS/MSI-L tumors. Dose the difference of the previous reports depend on the racial and/or environmental differences between Western and Asian populations, or the small number of patients with MSI-H tumors in this study? Additional larger studies may needed to clarify the modifying effect on the relation between BRAF mutations and survival outcome according to MSI status. These minor comments however shouldn't detract from well written report.

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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] 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	[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

REMS#:MS Number: 2014-12053 Title: "Prognostic value of KRAS and BRAF mutations in curatively resected colorectal cancer" by Kadowaki S. et al. Reviewer Comments: The authors have performed this study to investigate the prognostic value of KRAS and BRAF mutations after adjustment for MSI status in Japanese colorectal cancer population. This study is the first report concernig the prognostic value of KRAS and BRAF mutations in curatively resected colorectal cancer, and this will be the largest study to assess the prognostic value of k-ras and BRAF mutaion for survival outcome. They assessed KRAS and BRAF mutations and MSI status with curatively resected, stage I to III CRC and examined associations of these mutations with disease-free survival and overall survival using uni- and multivariate Cox proportional hazards models in a large scale, 813 Japanese patients. KRAS and BRAF mutations were detected in 312 (38%) of 812 and 40 (5%) of 811 tumors, respectively. After adjusting for relevant variables, including MSI status, KRAS mutations were associated with poorer DFS and OS. BRAF mutations were poor prognostic factors for DFS and OS. Neither the BRAF by MSI interaction test nor the KRAS by MSI interaction test yielded statistically significant results for DFS and OS. In conclusion, a KRAS and BRAF mutations are associated with poor survival, independent of MSI status, in Japanese patients with curatively resected CRC. More large scale randomized controlled trials is necessary to be carried out and confirm the findings. This manuscript shows the prognostic value of KRAS and BRAF mutation in curatively resected colorectal

cancer. Manuscripts are well written and shows significant novel findings. Indeed, this manuscript indicates the important characteristics of KRAS/BRAF mutation in Japanese CRCS-, but several critical points should be examined and manuscript should be revised. The critical comments are as followings; Specific comments: 1. Indeed MSI-H patiens are generally considered to be in good prognosis, but the results of this study does not correspond to these previous reports, suggesting that they may leads by the diffence of background in registration CRC cases? Author should add additional data or consideration in the discussion section. 2. Is there any reports concerning to the gender difference in KRAS/BRAF mutation incidence in the previous CRC research? The authors should discuss them in the manuscripts. 3. How about the anticancer drug sensitivity, especially EGFR inhibitior, in your institute? Please add the consideration with preliminary data.