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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 65300

Title: Histological differentiation impacts the tumor immune microenvironment in gastric carcinoma: relation to the immune cycle

Reviewer's code: 02367954
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: Portugal
Author's Country/Territory: Ukraine

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

In the present manuscript, Mashukov O et al characterised the tumour immune microenvironment of a series of 50 gastric cancers of different histological subtypes. The authors found interesting associations between histological subtypes of gastric cancer and the type of tumour immune microenvironment, which might help understanding the mechanisms of immune escape of gastric carcinomas, with potential predictive value for immunotherapy application. The paper is well written, with a clearly stated purpose. The methodology is adequate for the objectives of the study, the results are interesting and interpreted and discussed cleverly. The reviewer has some minor points and concerns that needed to be clarified and/or modified before publication: - The cohort analysed does not include any case of mixed gastric cancer. It could be interesting to elucidate the immune infiltration pattern of this subtype. Are the different components of mixed gastric cancer distinct, in terms of immunophenotype, or similar, as they (supposedly) have a common clonal origin? Is the immune context more similar to diffuse or intestinal type gastric cancer? It could be interesting to add a small group of mixed gastric cancers to discuss these points. - A table describing the general clinicopathological variable of the series is missing: age, sex, stage, histological type, grade (please remind that grading only applies to tubular and papillary subtypes), survival etc. - The clone used in this study to evaluate PD-L1 expression (E1L3N(R)) is not currently used in the clinical practice to select gastric cancer patients for immunotherapy. Please state this limitation in the study or, if possible technically, use the 22C3 antibody. - Abstract - Conclusion: "These data help to clarify the links among tumor histogenesis, molecular profile and immunogenicity for a better understanding of GC biology and more tailored patient management." Please consider eliminating "molecular profile" from the text, as the molecular profile of gastric cancer

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was not fully elucidated in this article (except for MMR protein deficiency). The same apply for "Core tip": "These data help to clarify the links among tumor histogenesis, molecular profile and immunogenicity." - MATERIALS AND METHODS - Tissue processing and immunohistochemistry: Modify MLH2 to MSH2 and MLH6 to MSH6 - MATERIALS AND METHODS - Methodology of tumor-host immunity assessment "The number of immunopositive cells was assessed as both continuous and dichotomized variables using cutoff values (84 cells per mm2 as a median)." It is not clear how the authors select the cut-off values. If the selection was based on the median value, should not the median value be different for each biomarker? Does 84 cells/mm2 refers to the CD8 counting? What about CD68 and CD163? Please clarify - RESULTS - TIL and TAM densities varied in GC of different histological types "Notably, GCs with a poor prognosis (mucinous and diffuse type) demonstrated a considerably higher M1/M2 ratio (Table 1)." This result is not represented in Table 1. - RESULTS - Immunophenotyping GC of different histological types "We did not find any statistically significant relationship between TIME and tumor grade (P = 0.523) or stage (P = 0.756)." Although there is not statistically significant difference, row data on tumour grade and stage should be presented, at least as supplementary file. - RESULTS - Immunophenotyping GC of different histological types "Inflamed TIME was more common for intestinal GCs, IE TIME prevailed in mucinous adenocarcinomas, and ID TIME was more typical for diffuse-type GC" This seems to be true looking at the row data. However, it would be great if the authors presented the statistical analysis for this assumption (see also table 3 – row data are presented, without a statistical comparison. At the beginning of the paragraph the authors refer a p value of <0.001, but the p value of each group is not expressed (should be a Bonferroni correction be performed?). - RESULTS - PD-L1 expression in GCs with different immunophenotypes "and CD163+ macrophages (P = 0,032)" please modify 0,032 to 0.032 - Figure 1. The quality of the

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images can be improved. Moreover, it would be better to present images representing the same magnification. - Figure 3. In C and D, it would be useful to indicate the p-value of the comparison between the two groups. “E” and “F” images are not shown in the panel submitted. - Table 1. “Mucinous e”. Please delete “e” - Table 1. "Shaded areas correspond to variables with statistically significant differences at the level P<0.05" Shaded areas are not visible in this table - Table 2. As stated above, the authors should present the comparison between different groups and respective p values