PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 75199

Title: Potential of six-transmembrane epithelial antigen of the prostate 4 as a prognostic marker for colorectal cancer

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03806663

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2022-01-18

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-02-01 13:22

Reviewer performed review: 2022-02-01 18:30

Review time: 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] 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	[Y] Yes [ ] No

| **Peer-reviewer statements** | Peer-Review: [Y] Anonymous   [   ] Onymous |
| | Conflicts-of-Interest: [   ] Yes   [Y] No |

SPECIFIC COMMENTS TO AUTHORS

This research discusses a hot topic in the field of colorectal cancer. 1- There are so many tumor markers used in the diagnosis, prognosis, and predictive factors in colorectal cancer, so what is the novelty of your work? 2-As regards images, please add scale bar, annotations, type of stain or dye, type of software program that generated these figures.

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SPECIFIC COMMENTS TO AUTHORS

Dear Authors, thank you for your interesting research. I have some comments which are below but overall I like the concept and the narration is pleasant to read. Some aspects need to be clarified, though. Thus, before further processing, please answer the and/or consider following: (1). The title of research could be more focused on STEAP4, although this is not obligatory. I see that you performed some preliminary research on all four family members but STEAP4 was then analyzed in detail. (2). In the "Core tip" you wrote that "STEAP4 is expected to be a novel therapeutic target for colorectal cancer" while the closing remarks indicate that it is rather a prognostic indicator/biomarker and moreover it was found downregulated in CRC and is presumably tumor suppressor, then how/why to subject it to targeted therapy? This contradicts the sentences like "Immunotherapy serves as an alternative treatment for cancer patients, especially for those whose tumors overexpress antigens recognized by immune cells" (if you would like to subject STEAP4 to this type of therapy then it is not overexpressed) as well as "STEAPs are present at the intercellular junctions of the prostate secretory epithelium, and are overexpressed in prostate cancer, serving as attractive targets for prostate cancer immunotherapy" (if STEAPs are overexpressed in PCa and serve as attractive targets then STEAP4 cannot be target in CRC since it is downregulated). To sum up, I would remove all sentences where STEAP4 was suggested as therapeutic target in CRC based on data from current study. (3). Could you please provide more details for methodology behind the step of visualizing MSI/MSS subtypes via TISIDB? Moreover, I would add link to TISIDB in this location, instead of the section later (alternatively, you can provide link in both sections where TISIDB is

mentioned in methodology). (4). Please add explanation of subfigures in the legends of figures 3 and 5. (5). Put the tables in tabular form, not as a pictures. (6). Please provide stain/dye type and scale in figure 4. (7). Above table 2 I would not write that "STEAP4 expression tended to be lower in CRC" because in this sections you only investigated clinicopathological parameters of CRC patients, not compared to normal tissues. Moreover, "tended to be lower" will not be in line with findings of the previous section where STEAP4 is clearly decreased in cancerous tissue which was statistically significant. (8). In table 3, if you put $p<0.05$ below table as a legend, then the p-values below $p<0.01$ should also be denoted as e.g. ** while in the table itself the precise values should be provided. Moreover, please add space between "table" word and the number, this refers to all tables. (9). What software was used to present Kaplan-Meier curves from Figure 8? I am also wondering whether the re-running the analysis but with DFS instead of OS would reveal some significant observations in terms of survival. Is this possible in your case and your data? Initially, please clarify why OS was used in methodology instead of DFS outcome? Events caused by disease recurrence occur earlier than death from the disease and moreover DFS also include tumors that do not necessarily lead to death, which are not included in OS. (10). Change "[...] assuming a potential tumor suppressor role of STEAP in CRC patients" to "[...] assuming a potential tumor suppressor role of this STEAP member in CRC patients" (it will sound better in my opinion, alternatively write "STEAP4" instead of just "STEAP" in this sentence). (11). Now, a slightly more complicated suggestion - I think that steps where all STEAPs are considered/visualized should be prior to focusing on STEAP4 only. This would give the deductive reasoning narration. (12). Last but not least, the usage of TIMER2.0 and then GEPIA2 for validation (figures 1-2) will most probably lead to the same or similar results as these databases use the same RNA-seq TCGA data, similar to step summarized in figure 6 (TISIDB and TIMER2.0 were compared). I think the slight differences might be

due to algorithm that is embedded in these databases to perform analysis. It would be much more preferred to validate the findings from RNA-seq TCGA using e.g. microarrays (see Xena database).

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Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

| **statements** | Conflicts-of-Interest: [   ] Yes   [Y] No |

SPECIFIC COMMENTS TO AUTHORS

Dear Authors, thank you for your revisions. Good work! I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology.