Dear Editor,

Thank you for carefully reviewing our manuscript titled "**Regorafenib combined with programmed cell death-1 inhibitor against refractory colorectal cancer and the predictive value of platelet-to-lymphocyte ratio on effectiveness**" for possible publication in the ***World Journal of Gastroenterology***. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, with changes tracked, and have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

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Reviewer #1:

1. You mentioned ECOG score in the manuscript. Usually it writes ECOG PS (performance status). Please check and revise those parts in whole manuscript.

Response: Thanks for your comment. We have changed "Eastern Cooperative Oncology Group (ECOG) score" to 'Eastern Cooperative Oncology Group (ECOG) performance status (PS)" for the first time use in the article and altered all the "ECOG score" in the manuscript to ECOG PS.

2. In the results part 3.1, you used >60 and <60. 60 years old case are not included this part. Please check and revise it like ≥.

Response: Sorry for this typing error. We have changed ">60 years" into" ≥60 years".

3. At figure 1 and figure 3, you wrote K-M figures. Usually, the researcher should write the number of patients under the K-M figures. Please check and revise those figures even if your sample size is small.

Response: Thanks for your comment. We have added the number of patients at risk in Figures 1 and 3.

4. At table 4, you wrote the number of patient and those percentages in the (). Please add its explanation first line of the table 4.

Response: Thanks for your comment. We have added the explanation at the first line of this table (Supplementary Table S1).

5. At figure 4, the authors did not mention the units of values. Please add the units all the figures here in figure 4.

Response: Thanks for your comment. We have added the unit (ug/ml) of CEA in the figure legend of Figure 4. As PLR is a ratio, it doesn't have an unit.

Reviewer #2:

1. In this study, four domestic anti-PD-1 inhibitors as well as nivolumab and pembrolizumab have been used. The authors should include discussion regarding the effect on treatment outcome according to different anti-PD-1 inhibitors.

Response: Thanks for your valuable suggestion. The number of patients with each domestic PD-1 inhibitor was limited in our study. Due to the national conditions and patients' financial burden, the number of patients who received nivolumab (n=3) or pembrolizumab (n=1) was also very low. Thus, we analyzed the difference in PFS between patients with imported PD-1 inhibitor (nivolumab or pembrolizumab) and those with domestic anti-PD-1 inhibitor (sintilimab, toripalimab, camrelizumab or tislelizumab), which showed no statistical significance. This comforting result was also supported by previous clinical trials of domestic PD-1 inhibitors. These have been added to the Discussion section.

2. Neutrophil-to-lymphocyte ratio did not predict the treatment efficacy. It would be better to discuss the reason for this result.

Response: Thanks for your valuable suggestion. An Italian study demonstrated that PLR was an independent factor influencing the outcomes of CRC [1]. Moreover, patients with high PLR also showed a high expression level of programmed cell death-ligand 1 (PD-L1) in circulating tumor cells, suggesting that PLR may also be a predictive marker of change in tumor immune microenvironment [1]. This may explain why PLR can predict the effectiveness of PD-1 inhibitor combination therapy, but NLR cannot. These have been added to the Discussion section.

References

1 **Raimondi L**, Raimondi FM, Di Benedetto L, Cimino G, Spinelli GP. PD-L1 Expression on Circulating Tumour Cells May Be Predictive of Response to Regorafenib in Patients Diagnosed with Chemorefractory Metastatic Colorectal Cancer. *Int J Mol Sci* 2020; **21**(18) [PMID: 32962309 PMCID: PMC7555209 DOI: 10.3390/ijms21186907]