Dear Editor and Reviewers:

Thank you very much for your letter and advice. we appreciate you very much for their positive and constructive comments and suggestions on our manuscript entitled "Efficacy and safety of preoperative PD-1 blockade immunotherapy in patients with dMMR/MSI-h gastrointestinal malignancies" (Manuscript ID 81795). Those comments are all valuable and very helpful. We have studied comments carefully and have made correction which we hope meet with approval. Below we provide a point-to-point response to the comments:

Reviewer #1:

Main Comments: This manuscript deals with preoperative PD-1 blockade immunotherapy in patients with dMMR/MSI-H gastrointestinal malignancies. The presented evaluation has the drawbacks of a retrospective study design. More details of the study protocol are required (name of the drug(s)?, consistent treatment regimen(s)?, control group?). Shortcomings also include heterogeneity, small sample size and short follow-up periods.

Answer: Thank you for your worthy comment. We agree with the reviewer. Revised: We added name of the drug and consistent treatment regimen in Table 2. according to your suggestion. Our study has some limitations. First, the sample size is relatively small, and it describes real-world cases rather than a prospective RCT design--patients administered PD1 drugs for specific reasons such as a huge tumor, organ preservation, and the regimen is not limited to fixed treatment cycles. Although limited to the number of cases, it uncovered the tip of the iceberg of neoadjuvant immunotherapy for dMMR/MSI-H gastrointestinal malignancies in real-world setting. Second, the follow-up time after surgery was relatively short, so the long-term efficacy is waiting for further confirmation.

Additional Comments/Suggestions: "dMMR/MSI-h" and "dMMR/MSI-H" – please be consistent (throughout the whole manuscript). Page 3, last paragraph: "pembrolizumab (programmed death protein (PD)1 blockade]" -> pembrolizumab [programmed death protein (PD)1 blockade]. Page 4, first paragraph: "compete response (CR)" -> complete response (CR). Table 3: "Surgery-realted" -> Surgery-related. Page 10, last paragraph: "did not required surgery" -> did not require surgery. The reference list needs revision; parts of it are not consistent with the guidelines of the journal, references 1 and 8 are identical, etc.

Answer：Thank you very much for your detailed and earnest comments. You are right. I apologize for my negligence so much. Revised：We have made changes and corrections for spelling errors and references

Thank you very much for your detailed and earnest comments. I appreciate so much. We have revised them point by point. They are very valuable for us. Thank you.

Reviewer #2:

Specific Comments to Authors: This manuscript Is not adapt to publication due to some major systematic errors and need a more stronger statistical analysis.

Answer: Thank you for your worthy comment. We revised the manuscript in more detail and asked statisticians to correct errors.

Thank you very much for your detailed and earnest comments. They are very valuable for us.

Thank you.

Reviewer #3:

Comments 1-Please explain the differences between pCR and cCR in a more detailed way.

Answer: Thank you for your constructive suggestion. We have added the criterion of pCR and cCR. The cCR was defined as no evidence of residual tumor determined by rectum MRI, abdomen/pelvis CT and chest CT, endoscopic physical examination, nomarl CEA and/or digital rectal exam. Pathological staging was based on the 8th edition of the American Joint Committee on Cancer TNM staging system. Post-treatment response was assessed by NCCN grading:0 = complete response (ypCR) with no detectable cancer cells; 1 = major response with few residual cancer cells; 2 = partial response; 3 = no or very little response.

Comments 2-Material and methods, Treatment and evaluation All patients received PD1 blockade (PD1 blockade 200 mg intravenously). Please add the name of the PD1 blockade drug used. What was the schedule of administration of PDF 1 blockade?

Answer: Thank you very much for your detailed and earnest comments. I appreciate so much. Revised: We added name of the drug and consistent treatment regimen in Table 2.

Comments 3-"Six patients received 2–10 cycles of adjuvant mono-immunotherapy after reaching cCR " Which were the criteria for repeating the cycles of adjuvant mono immunotherapy? it has not been explained either in material and methods or in the results

Answer: Thank you for your valuable comment and information. Currently, there is no standard postoperative adjuvant therapy for MSI-h gastrointestinal malignancies. We performed the treatment according to our experience after judging cCR. The sample size of this retrospective study was small. Our data are preliminary and need to be confirmed by more cases.

Comments 4-Results TABLE 2, What means: rectectomy?, perhaps "proctectomy or Low anterior resection." What does CLM stand for? What does ICB stand for? "

Answer: Thank you very much for your detailed and earnest comments. You are right. I apologize for my negligence so much. Revised： We add a note in TABLE 2.

TABLE 2.((LACC= Locally Advanced Colon Cancer, pMMR=proficient mismatch repair, dMMR=different mismatch repair, ICB=Immune checkpoint inhibitor, CLM=Colorectal Liver Metastases, LAR= Low Anterior Resection.)

Comments 5-cCR was achieved in 7/36 cases, among which six were selected for wait and watch strategy,.." Which one were these patients: 3 duodenum tumors, three low rectum, and 1 CLM "metastatic" ? This paragraph is a little challenging to understand:" All three patients with locally advanced gastric cancer achieved pathological CR (pCR). All three patients with locally advanced duodenal carcinoma achieved cCR and then watch and wait (Video 1)…..CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. The CR (cCR and pCR) rate was 58.3%(21/36)". It would be possible to add some information to table II with a new item, such as locally advanced colon cancer.

Answer: Thank you for your constructive suggestion. Revised: We marked specific patients. cCR was achieved in seven patients(patient 4,5,6,23,26,27,30), among which six(patient 4,5,6,23,26, 30) were selected for wait and watch strategy. Three patients with locally advanced gastric cancer achieved pathological complete response (pCR). Three patients with locally advanced duodenal carcinoma achieved clinical complete response (cCR). We added locally advanced colon cancer(LACC) to table II with a new item.

Comments 6-Please add some thoughts about the surgical complications such as perforation, obstruction, or enlargement of lymph nodes without metastatic connotations, perhaps as an inflammatory or necrosis process related to the immune response.
Answer: Thank you for your constructive suggestion. We added thoughts about the surgical complications. Unlike chemoradiotherapy and targeted therapy, one of the characteristics of immuno-neoadjuvant therapy is that imaging and pathological evaluation results may vary considerably. Due to immune cell infiltration and other reasons, many patients did not observe tumor remission on imaging-maintained stability or even some enlargement, but pathological examination will find a large number of necrosis tumors and inflammatory immune response. Our study also observed this phenomenon.

Thank you very much for your detailed and earnest comments. I appreciate so much. We have revised them point by point. They are very valuable for us. Thank you.

Special thanks to you for your good comments. We hope the manuscript is now acceptable for publication in your journal.

I'm looking forward to hearing from you soon.

Your sincerely, Yingjie Li & Aiwen Wu