Peer Review File

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Reviewer A

Fruquintinib and anti-PD-1 antibody showed efficacy for refractory mCRC for liver in this study. As liver is the most frequent metastatic region for CRC, its impact is valuable. Combination therapy using fruquintinib with anti-PD-1 antibody might contribute therapy for patients suffering from mCRC with liver metastasis. However, minor revisions are needed for publication as mentioned belows.

Comment 1: In the discussion historical results after fruquintinib or anti-PD-1 antibody should be mentioned in detail.

Reply 1: we have modified our text as advised (see page 11, line 321-326)

Comment 2: You must be careful to note references according to the guideline. Almost all references not met guideline.

Reply 2: we have modified the references met guideline.

Reviewer B

Comment 1: the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study.

Reply 1: we have modified our title as advised (see page 1, line 5)

Comment 2: the abstract needs some revisions. The background did not have comments on the limitations of prior studies and what the current knowledge gap is. The methods need to describe the inclusion criteria of subjects, the assessment of baseline clinical factors, follow up procedures, and measurements of efficacy and safety outcomes. The results need to briefly summarize the clinical characteristics of the study sample and report safety outcomes. The comments need to have comments on the clinical implications of the findings.

Reply 2: we have modified our abstract as advised (background: see page 2, line 58-60; methods: see page 66-70; results: see page 3, line 76-85; conclusion: see page 3, line 88-91)

Comment 3: the introduction of the main text needs to review what has been known on the efficacy and safety and their predictors of PD-1 inhibitors for MSS CRC, analyze the potential reasons for inconsistent findings, and clearly indicate the novelty and strengths of this research. In particular, the authors emphasized real-world, but they did not explain the needs for real-world data.

Reply 3: we have modified our introduction as advised (see page 5, line 141-150; line 155-162;

line 164-166)

Comment 4: in the methodology of the main text, please describe the clinical research design, sample size estimation, assessment of baseline clinical factors, and details of follow up. In statistics, it is wrong to describe “The number of cases in the Hunan Cancer Hospital during the study period determined the sample size”. In statistics, please ensure $P<0.05$ is two-sided.

Reply 4: we have modified our methodology of the main text, add the describe the clinical research design and sample size estimation (sample size estimation: see page 7-8, line 231-236; clinical research design: page 6-7, line 180-192; 199-202; assessments: page 7, line 210-212)

Comment 5: Please consider to cite several related papers:

1. Ma S, Chen R, Duan L, Li C, Yang T, Wang J, Zhao D. Efficacy and safety of toripalimab with fruquintinib in the third-line treatment of refractory advanced metastatic colorectal cancer: results of a single-arm, single-center, prospective, phase II clinical study. J Gastrointest Oncol 2023;14(2):1052-1063. doi: 10.21037/jgo-23-108.
2. Dai Y, Sun L, Zhuang L, Zhang M, Zou Y, Yuan X, Qiu H. Efficacy and safety of low-dose apatinib plus S-1 versus regorafenib and fruquintinib for refractory metastatic colorectal cancer: a retrospective cohort study. J Gastrointest Oncol 2022;13(2):722-731. doi: 10.21037/jgo-22-285.
3. Li L, Wang T, Wu Z, Li Y, Ma H, Wang L, Lei S, Chen W. Fruquintinib in combination with sintilimab or TAS-102 as third-line or above treatment in patients with metastatic colorectal cancer: a real-world study. Transl Cancer Res 2023;12(11):3034-3044. doi: 10.21037/tcr-23-867.

Reply 5: we have add the related papers (1: see page 5, line 159, reference 20; 2: see page 4, line 114, reference 6; 3: see page 4, line 114, reference 8)