
Peer Review File

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Reviewer A

This is a case report demonstrating meaningful clinical benefit to fruquintinib + PD-1 inhibitor in a treatment-refractory mCRC. Although the OS of 54 months is not too exciting in the setting of a L-sided RAS/BRAF WT mCRC, the serologic response and discussion on response to liver metastases but not really liver metastases is interesting for publication.

I have the following revision requests:

Would cite recent data supporting VEGF-TKI + IO combinations in MSS mCRC with a focus on lack of response in liver metastases but with greater responses in lung metastases as it relates to this case.

Reply: We have cite and discussed some related data such as references of 17 to 19.

Changes in the text: none.

Line 80: Would correct the sentence: "Therefore, the immunotherapy of pMMR CRC remains a great challenge." to something like the "establishment of immunotherapy in pMMR..."

Reply: Thanks for your good suggestion. We have modified our text as advised with "Therefore, establishment of immunotherapy in pMMR remains a great importance".

Changes in the text: Page 3, line 80.

Line 223: For the sentence: "Hence, we recommend fruquintinib combination immunotherapy for patients with MSS mCRC, especially with lung metastases, and patients with liver metastases are also recommended to this treatment if their economic status and physical strength are conducive." Would add a sentence that local therapy to the liver may be indicated given the immune sink nature of colorectal liver metastases with an inclusion of a reference.

Reply: We have added a sentence in our text as advised with "The local therapy to the liver may be indicated given the immune sink nature of liver metastases in colorectal cancer".

Changes in the text: Page 7, line 225.

Reviewer B

1) First, the title needs to indicate that this is a case report.

Reply: We have added "case report" in the title.

Changes in the text: Page 1, line 5.

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- 2) Second, the abstract needs some revisions. The background did not explain the potential unique clinical contribution of this case report and why the current case deserved to be reported. The case presentation part needs more data on the clinic-pathological characteristics of this case and findings on the safety and adverse events of this case during the treatment. The current conclusion needs to be tone down since this is only a case report, not clinical trials.

Reply: We have modified our abstract as advised.

Changes in the text: Page 2, line 33-57.

- 3) Third, in the introduction of the main text, the authors need to review all possible treatments for pMMR CRC and analyze the fruquintinib plus anti-PD-1 immunotherapy is potentially effective and safe. Please also analyze why the current case deserved to be reported and what its unique clinical contribution is.

Reply: We have modified our text: This report shows that a patient with MSS mCRC **achieved a significant response and the longest PFS with 28 months currently reported** from fruquintinib plus anti-PD-1 immunotherapy as the third treatment line, which gives people more confidence in the new combination regimen.

Changes in the text: Page 4, line 99.

- 4) Fourth, in the case presentation, please report more clinical findings on the health and functional status of this case such as the nutritional status, BMI, and immune biomarkers, as well as co-occurring physical health problems. Please toned down the current conclusion since this is only a case report with poor external validity.

Reply: We have added: Throughout the treatment period, this patient had good functional status with an Eastern Cooperative Oncology Group (ECOG) performance status of 1, Body mass index (BMI) of 24.2 and Nutritional Risk Screening 2002 (NRS 2002) of 0.

Changes in the text: Page 5, line 155.

- 5) Finally, please consider to cite some related papers: 1. Deng YY, Chen YW, Wang MX, Zhu PF, Pan SY, Jiang DY, Chen ZL, Yang L. Acute aortic dissection caused by fruquintinib for metastatic colorectal cancer—a case report and literature review. *Transl Cancer Res* 2023;12(1):177-185. doi: 10.21037/tcr-22-1872. 2. Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. *Transl Cancer Res* 2022;11(1):276-287. doi: 10.21037/tcr-20-3539. 3. Wang Y, Li J, Xu Q, Li K, Zhang C, Chen P. Fruquintinib for refractory colorectal cancer in a pre-treated 82-year-old patient achieved a progression-free survival of 25 months: a case report. *J Gastrointest Oncol* 2022;13(5):2667-2671. doi: 10.21037/jgo-22-841. 4. 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.

Reply: We have added No.2 and 4 paper as reference 9 and10.

Changes in the text: Page 6, line 180.

Reviewer C

1. References

Please confirm if citations are missing in the sentence, as you mentioned “studies”.

References should be cited consecutively and consistently according to the order in which they first appear in the text.

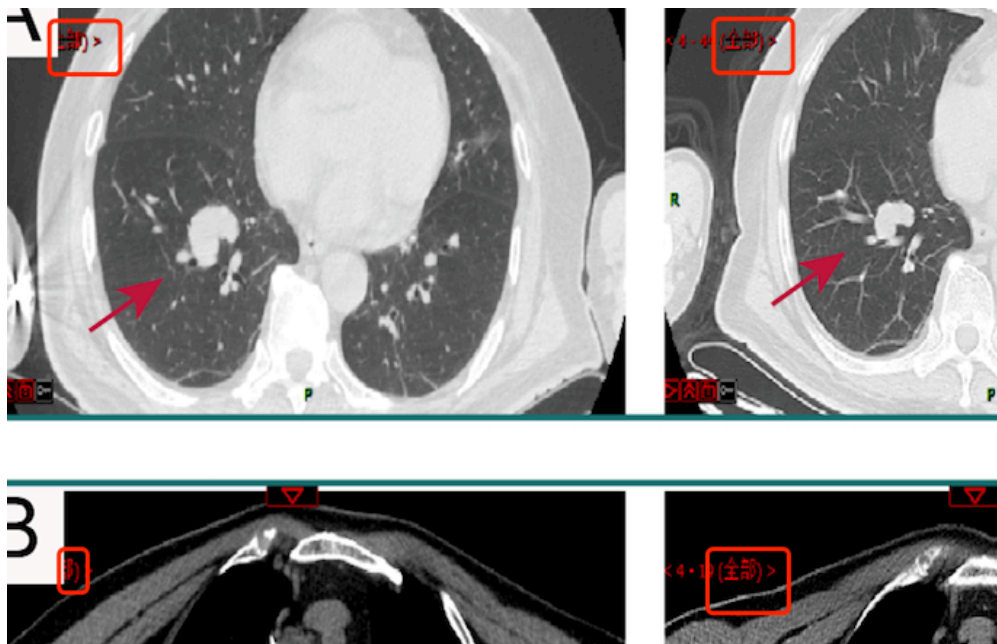
Studies have shown that combination of fruquintinib and PD-1 inhibitors can synergistically inhibit the progression of colorectal cancer cells, change the tumor microenvironment, and promote immune antitumor activity.

Pharmacokinetic studies have shown that fruquintinib is mostly metabolised in the liver, with subsequent biliary and renal-predominant excretion.

Reply: I have added References for the two sentence.

2. Figure 2 and Figure 3

There are some Chinese characters in images. Please remove them.



Reply: I have revised these Chinese characters .

3. Figure 3

It is “11” in figure legend, but it is “15” in image A. Please check and revise.

562 Figure 3 Abdominal CT scanning. Abdominal CT scanning showed uneven decrease
 563 in liver density, with scattered round low density shadows in the right lobe of the liver.
 564 The maximum diameter was estimated to be about 30 mm before the third-line
 565 treatment on October 11, 2019 (A), and then it was almost unchanged with size of 30



Reply: I have revised the time in legend of figure 3.

4. Figure 4A-D and Figure 5A-I

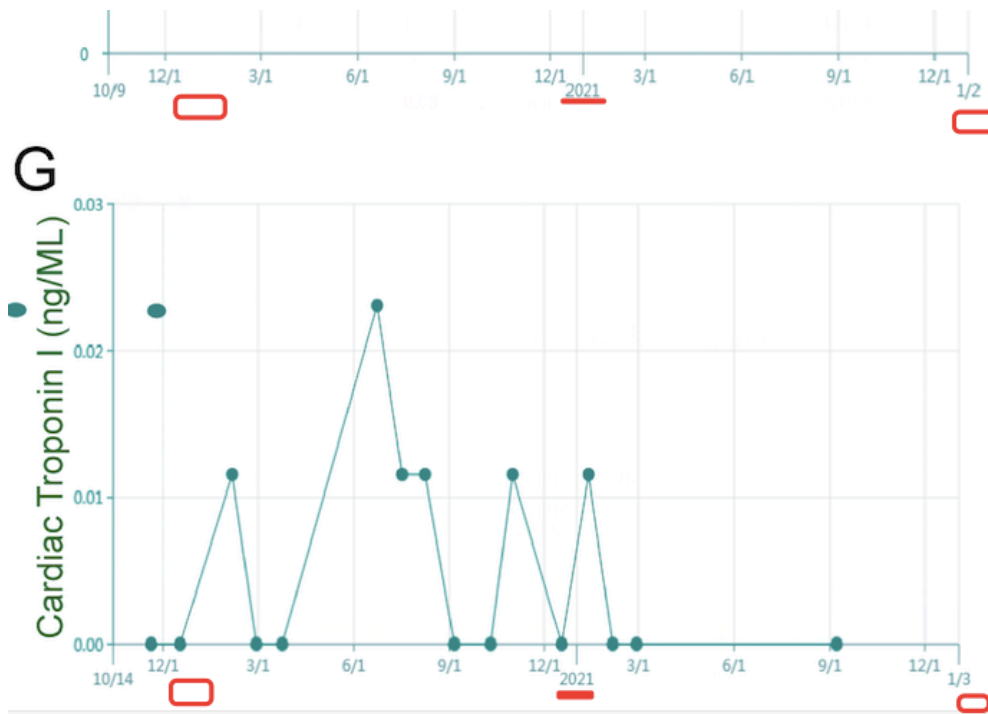
a. Please add the description to the X-axis.



Reply: I have add the description to the X-axi in Figure 4-revised and Figure 5-revised.

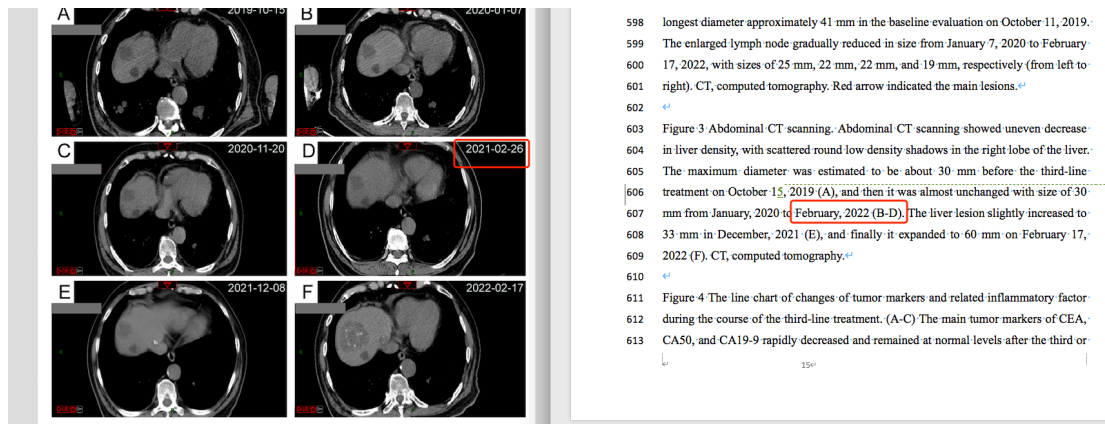
b. The year '2020, 2022' are missing in some X-axis. Please check each panel, and revise.





Reply: I have add the description of time.

5. Figure 3D
2021 or 2022? Please check and revise.



Reply: I have revised the time in legend of figure 3D.