Peer Review File

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Reviewer A

Comment 1: The authors comment that: In previous studies, we found that the majority of patients were intolerant to oral administration of fruquintinib 5 mg qd; therefore, in this study, fruquintinib was administered orally 4 mg qd, d1-21, every 28 days as a cycle.

=>The dose of fruquintinib used for the study was 4mg while most studies used 5mg. It would be helpful to show how this compared to other doses as far as efficacy and toxicity shows.

Reply 1: In previous studies, we found that the majority of patients were intolerant to oral administration of fruquintinib 5 mg qd; therefore, in this study, fruquintinib was administered orally 4 mg qd, d1-21, every 28 days as a cycle.

Changes in the text: Line 229-231

Comment 2: The authors mention "Forty-seven mCRC patients received fruquintinib combined with sintilimab (FS group), and 45 mCRC patients received fruquintinib combined with TAS-10 (FS group)."

=>How were the patients assigned to either of the two groups? Was this per Provider preference? It would be helpful to clarify group assignment criteria here.

Reply 2: SAS statistical analysis system was used to generate random numbers and formed a random coding table. Patients were strictly enrolled according to the corresponding random coding table and assigned to FS group and FT group.

Changes in the text: Line 98-101

Comment 3: The number of right colonic metastatic sites ranged from one to two in 48 patients (52.2%), while the number of metastatic sites ranged from three to more in the other 44 patients (47.8%).

=>Please correct the sentence to reflect which side (left or right) is involved in the latter part of the sentence: "while number of metastatic sites ranged from three to more in the other 44 patients (47.8%)"

Reply 3: The number of colonic metastatic sites ranged from one to two in 48 patients (52.2%), while the number of metastatic sites ranged from three to more

in the other 44 patients (47.8%).
Changes in the text: Line 139

Comment 4: The study population had 18% total, 12% FS, 6% patients aged more than or equal to 65 years only. This shows a much more younger population cohort. It would be good to include that as a caveat while interpreting results given that trials such as FRESCO-2 for instance had 46% of patients aged more than or equal to 65 who received Fruquintinib.
Reply 4: In this study, 18 patients (19.6%) were older than or equal to 65 years old, including 12 patients (25.5%) in FS group and 6 patients (13.3%) in FT group. Compared with studies such as fresco-2, 46% of patients older than or equal to 65 years old were treated with furquitinib. Younger patients were included in this study.
Changes in the text: Line 275-278

Comment 5: BRAF was mutated in 2 patients who received FS and 4 in patients who received FT; however per the previous lines of treatment documented there is no mention of BRAF inhibitor treatment. It would be helpful to verify this information.
Reply 5: The six patients with BRAF gene mutations (2 in FS group and 4 in FT group) included in this study had not received BRAF inhibitor treatment.
Changes in the text: Line 149-151

Comment 6: "The DCRs of the FS group and FT group were 80.9% (38/47) and 55.6% (25/45), respectively, and the DCR of the FS group was higher than that of the FT group (P=0.009)" mentioned by the authors are impressive but primarily driven by the difference in stable disease in 30 vs 19 patients (FS vs FT respectively). It would be important to make this clear distinction as a comment.
Reply 6: The DCRs of the FS group and FT group were 80.9% and 55.6%, respectively (p=0.009), but there was no significant difference in ORR between FS group and FT group (p>0.05); This result may be mainly related to 30 patients and 19 patients with curative effect of SD (FS and FT). For patients with metastatic colorectal cancer who fail or are intolerant to second-line or above treatment, it was also a gratifying result for researchers to achieve SD in third line or above treatment.

Changes in the text: 261-264

Comment 7: 55.3 FS vs 60% FT group with liver mets while on FRESCO 66.5% on F and FRESCO2 study 74% had liver metastasis. It would be interesting to see what the comparison is between patients with and without liver metastasis and if that impacts outcomes. Per this study from ESMO, Pts with liver metastases had lower ORR than those without (7.1% vs 33.3%, P=0.0398): https://oncologypro.esmo.org/meeting-resources/esmo-congress/fruquintinib-plus-sintilimab-in-refractory-repair-proficient-pmmr-microsatellite-stable-mss-metastatic-colorectal-cancer-mcrc-preliminary-cl

Reply 7: 53 patients with liver metastasis were included in this study. In the FS and FT groups, there was no statistical difference in ORR between patients with liver metastasis and patients without liver metastasis (p>0.05), which was inconsistent with the findings of W. Zhang, et al(34) (whether it was related to different doses of fruquintinib).

Changes in the text:265-268

Comment 8: It would be helpful to include duration of treatment on both regimens, median follow up and how many patients required drug discontinuation or dose reduction to have a better understanding of tolerance.

Reply 8: The median follow-up time of the study was 10.791 months. All patients were treated with fruquintinib combined with sintilimab or TAS-102 until unacceptable toxicity, disease progression or death occurred.

Changes in the text:181-183

Comment 9: “The Phase IB of Abstract 2514 trial of fruquintinib combined with sintilimab foradvanced colorectal cancer was released by ASCO in 2021.”

=>Recommend inclusion of citation for this trial.

Reply 9: 30. Ye Guo, Weijie Zhang, Jieer Ying, et al. Preliminary results of a phase 1b study of fruquintinib plussintilimab in advanced colorectal cancer. Journal of Clinical Oncology 2021;39:2514-14

Changes in the text:272,370-371

Comment 10:

Recommend review of following articles for the discussion section:

1) https://www.sciencedirect.com/science/article/pii/S0140673623007729:

Arvind Dasari, Sara Lonardi, Rocio Garcia-Carbonero, Elena Elez, Takayuki Yoshino, Alberto Sobrero, James Yao, Pilar García-Alfonso, Judit Kocsis, Antonio Cubillo Gracian, Andrea Sartore-Bianchi, Taroh Satoh, Violaine Randrian, Jiri Tomasek, Geoff Chong, Andrew Scott Paulson, Toshiki Masuishi, Jeremy Jones, Tibor Csőszi, Chiara Cremolini, Francois Ghiringhelli, Ardaman Shergill, Howard S Hochster, John Krauss, Ali Bassam, Michel Ducreux, Anneli Elme, Laurence Faugeras, Stefan Kasper, Eric Van Cutsem, Dirk Arnold, Shivani Nanda, Zhao Yang, William R Schelman, Marek Kania, Josep Tabernero, Cathy Eng,

Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study,

The Lancet,

Volume 402, Issue 10395,

2023,

Pages 41-53,

ISSN 0140-6736,

https://doi.org/10.1016/S0140-6736(23)00772-9.

Reply 10: 38. Arvind Dasari, Sara Lonardi, Rocio Garcia-Carbonero, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet 2023; 402: 41-53

Changes in the text:277, 292-294

2)

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.917353/full

AUTHOR=Nie Caiyun, Lv Huifang, Chen Beibei, Xu Weifeng, Wang Jianzheng, Liu Yingjun, Wang Saiqi, Zhao Jing, He Yunduan, Chen Xiaobing

TITLE=Microsatellite stable metastatic colorectal cancer without liver metastasis may be preferred population for regorafenib or fruquintinib plus sintilimab as third-line or above therapy:A real-world study

JOURNAL=Frontiers in Oncology

VOLUME=12

YEAR=2022

URL=https://www.frontiersin.org/articles/10.3389/fonc.2022.917353

DOI=10.3389/fonc.2022.917353

Reply 10: 14. Nie Caiyun, Lv Huifang, Chen Beibei, et al. Microsatellite stable metastatic colorectal cancer without liver metastasis may be preferred population for regorafenib or fruquintinib plus sintilimab as third-line or above therapy:A real-world study. Frontiers in Oncology 2022;12:917353

Changes in the text: 70, 332-334

3) https://www.ejcancer.com/article/S0959-8049(22)01792-0/fulltext

AUTHOR=Nie Caiyun, Lv Huifang, Chen Beibei, Xu Weifeng, Wang Jianzheng, Liu Yingjun, Wang Saiqi, Zhao Jing, He Yunduan, Chen Xiaobing

TITLE=Microsatellite stable metastatic colorectal cancer without liver metastasis may be preferred population for regorafenib or fruquintinib plus sintilimab as third-line or above therapy:A real-world study

JOURNAL=Frontiers in Oncology

VOLUME=12

YEAR=2022

URL=https://www.frontiersin.org/articles/10.3389/fonc.2022.917353

Reply 10: 14. Nie Caiyun, Lv Huifang, Chen Beibei, et al. Microsatellite stable metastatic colorectal cancer without liver metastasis may be preferred population for regorafenib or fruquintinib plus sintilimab as third-line or above therapy:A real-world study. Frontiers in Oncology 2022;12:917353

Changes in the text:70, 332-334

4) https://oncologypro.esmo.org/meeting-resources/esmo-congress/fruquintinib-plus-sintilimab-in-refractory-repair-proficient-pmmr-microsatellite-stable-mss-metastatic-colorectal-cancer

Fruquintinib plus sintilimab in refractory repair proficient pmmr microsatellite stable mss metastatic colorectal cancer

Reply 10: 34. W. Zhang, Y. Sun, Z. Jiang, et,al. Fruquintinib plus sintilimab in refractory repair-proficient (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC): Preliminary clinical results and biomarker analyses from a phase II study. Annals of Oncology 2022;33:S136-S196.

Changes in the text: 267, 381-383

Reviewer B

1. Reference
   (1) The citations of ***Ref 20-22 and 36*** are missing in the text, please check and revise.
   The above references have been revised.
   (2) Please check if any references should be cited in the following sentence since you mentioned "previous studies".
   - In previous studies, we found that the majority of patients were intolerant to oral administration of fruquintinib 5 mg qd (the majority of adverse events included hepatic toxicity, hand-foot syndrome, etc);

   In our previous study of a few cases, we found that the majority of patients were intolerant to oral administration of fruquintinib 5 mg qd in Combination with Sintilimab or TAS-102. These results were not published publicly.

2. Figures and tables
   (1) Please supplement the table head in Tables 1,3 and 4.

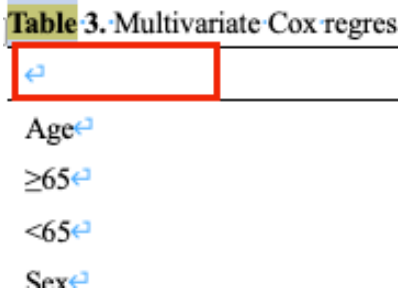
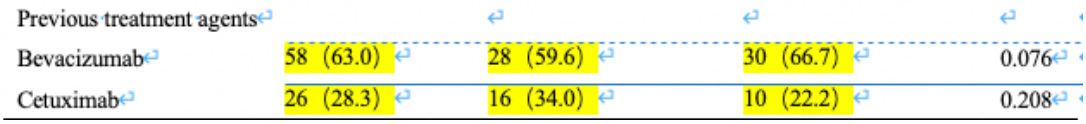


Table 3. Multivariate Cox regres

Age	
≥65	
<65	
Sex	

   The table head in Tables 1,3 and 4 has been suppled.
   (2) Please add a unit after Age in Table 1 and 3.
   The unit after Age in Table 1 and 3 has been added.
   (3) Please below data in Table 1, which are not equal to the total number of each item.



Previous treatment agents				
Bevacizumab	58 (63.0)	28 (59.6)	30 (66.7)	0.076
Cetuximab	26 (28.3)	16 (34.0)	10 (22.2)	0.208

   These issues have been confirmed. Targeted therapy included anti-VEGF therapy (bevacizumab, 58 patients, 63.0%) and anti-EGFR therapy (cetuximab, 26 patients, 28.3%). In the previous treatment, some patients received bevacizumab, some patients received cetuximab, some patients received the above two targeted therapies, and some patients did not receive the two targeted therapies.
   (4) Please indicate how data is presented in Table 4.
   Table 4 has been modified.
   (5) Table 1: please check below treatment lines, inconsistent with your main text.

Treatment line		
3	43 (46.7)	21 (44.7)
≥4	49 (53.3)	26 (55.3)

167 (47.8%). Forty-three patients (46.7%) had received two previous antineoplastic treatment regimens,
168 and the remaining 49 patients (53.3%) had received three or more. All patients enrolled in this study

The number of treatment lines in the text has been modified: Fruquintinib plus sintilimab or TAS-102 were given as third-line therapy in 43 (46.7%) patients, and as fourth-line or above therapy in the other 49 (53.3%) patients.

(6) The below should be Table 4.

214 The majority of adverse events (AEs) were grade 1-2 in severity and generally well tolerated. AEs
215 are presented in Table 3. The most common grade 3 or above AEs were anemia (4.3% in the FS

This modification has been confirmed.

(7) There is a spelling mistake in Figure 1. And please add unit % in the y-axis.

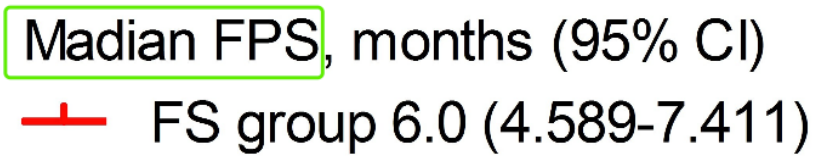


Figure 1 has been modified.