Peer Review File

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Reviewer A

Authors conducted a narrative review to compare the efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer from randomized controlled trials (RCTs) and observational studies by a literature search in PubMed, and SCI indexed journals.

Major Compulsory Revisions:

Comment 1: Some recent meta-analyses articles including 1. Comparison of Regorafenib, Fruquintinib, and TAS-102 in Previously Treated Patients with Metastatic Colorectal Cancer: A Systematic Review and Network Meta-Analysis of Five Clinical Trials. Med Sci Monit. 2019;25:9179-9191; 2. A comparison of regorafenib and fruquintinib for metastatic colorectal cancer: a systematic review and network meta-analysis. J Cancer Res Clin Oncol 2019;145(9):2313-2323; 3. Comparison of efficacy and safety for patients with beyond second line treated metastatic colorectal cancer: a network meta-analysis of randomized controlled trials. J Chemother 2020;32(4):163-170; 4. Regorafenib, TAS-102, or fruquintinib for metastatic colorectal cancer: any difference in randomized trials? Int J Colorectal Dis 2020;35(2):295-306; therefore, the current study just described the already known results but no more new information for readers.

Reply 1: Thank you for the comment. We acknowledge the fact that regorafenib and fruquintinib were previously compared in meta-analysis and network meta-analysis after systematic review in patients with CRC. However, all the published meta-analysis included only RCT evidence for statistical analysis. While RCT evidence may provide good internal validity, in case of CRC, the patient age group in RCT settings cannot reflect real-world age distribution. Meta-analysis of real-world evidence has not been performed for comparing regorafenib and fruquintinib mainly because of the unavailability of real-world evidence for assessing the effectiveness of fruquintinib. Hence, in this narrative review we have summarized the RCT and real-world evidence for assessing regorafenib and fruquintinib which was not done in previous meta-analysis. Also, the heterogeneity with respect to age in the different

RCTs cannot be accounted for satisfactorily in meta-analysis. Further, while the previous studies also included other drugs like TAS-102, the current narrative review, included only of action. This is of significance since current fruquintinib and regorafenib since both have similar modes studies are also evaluating the combination of angiogenic inhibitors and programmed death ligand-1 inhibitors.

A part of this explanation has been included in the revised manuscript.

Changes in the text: Page 14-15 Line 333-343

"Although previous meta-analyses have compared the efficacy of regorafenib and fruquintinib, they had included only RCT evidence for statistical analysis. Although RCT evidence may provide good internal validity, in case of CRC, the patient age group in RCT settings cannot reflect real-world age distribution. Meta-analysis of real-world evidence has not been performed for comparing regorafenib and fruquintinib primarily because of the nonavailability of real-world evidence for assessing the effectiveness of fruquintinib. Moreover, the heterogeneity with respect to age in the different RCTs cannot be accounted for satisfactorily in meta-analysis. Further, while previous studies also included other drugs such as TAS-102, the current narrative review included only fruquintinib and regorafenib as both have similar modes of action. This is of significance considering that current studies are also evaluating the combination of angiogenic inhibitors and programmed cell death ligand-1inhibitors."

Comment 2: As regorafenib and fruquintinib have shown better efficacy when compared to placebo in clinical trials leading to their FDA approval; however, there is no evidence based on direct comparison. Based on criticism 1, this sentence should be amended.

Reply 2: Thank you for the comment. Kindly note that the previous studies highlighted in criticism 1 were indirect comparisons performed with a common comparator. Nevertheless, to avoid ambiguity we have revised the text as mentioned below.

Changes in the text: Page 2 Line 31-37

"On the other hand, fruquintinib inhibits signaling through the vascular endothelial growth factor receptors family. Regorafenib and fruquintinib have both received United States Food and Drug Administration approval for treating metastatic colorectal cancer in patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an

anti- vascular endothelial growth factor therapy, and Rat sarcoma wild type, an anti-epidermal growth factor receptor therapy."

Page 15-16 Line 371-373

"The results are awaited from a real-world study of regorafenib versus fruquintinib in CRC (NCT04431791), which will provide clarity on their clinical benefits."

Comment 3: Data for fruquintinib has only been evaluated in Chinese population, and is not recommended in other countries or NCCN or ESMO guideline?

Reply 3: Since Fruquintinib has gained FDA approval recently for mCRC, trials are ongoing across the globe in different populations, we have mentioned the trials in our section "Future Perspectives".

Changes in the text: Page 15 Line 354-365

"A dose-escalation, multicenter non-RCT in the United States (US) evaluating the toxicity and anticancer activity of fruquintinib in patients with advanced solid tumors (NCT03251378) revealed that the anticancer activity, safety profile, and tolerability of fruquintinib were congruous with other anti-angiogenic TKIs. The recommended phase 2 dose of 5 mg once daily in US patients is similar to that in Chinese patients; the dose-expansion phase of the study is still ongoing (58). FRESCO-2 (NCT04322539 and EudraCT: 2020-000158-88) is another key study evaluating the efficacy and safety of fruquintinib in patients with refractory mCRC. It is a randomized, phase 3 study being held at 136 locations, with recruitment in the US, Europe, Australia, and Japan. A total of 687 patients with progression on or intolerance to trifluridine–tipiracil and/or regorafenib and previously treated with chemotherapy will be randomized to either fruquintinib or placebo in conjunction with best supportive care. This study will determine the OS and PFS and provide valuable insights into a diverse population (59)."

Comment 4: Regarding narrative review checklist: Research selection did not comply with the request (Page 21).

Reply 4:

Thank you for the comment. We have included a section on study selection and the checklist

has been updated accordingly.

Changes in the text: Page 4 Line 87-91

“Literature search was done on PubMed for articles published in English focusing on articles related to efficacy and safety of regorafenib and fruquintinib. The keywords ‘regorafenib’ OR ‘Fruquintinib’ AND ‘colorectal cancer’ for clinical studies performed in randomized controlled settings and real-world settings were used.”

Comment 5: mCRC patients at 3rd-line therapies might have the benefits to receive cetuximab plus chemotherapeutic agents, how is the role of cetuximab plus chemotherapeutic agents in mCRC patients beyond second line treatment? Authors are suggested to describe this point in the manuscript.

Reply 5: The comment was noted and the following text was added under the section “targeting angiogenesis in CRC”.

Changes in the text: Page 5 Line 106-117

“According to a systematic review and meta-analysis of 12 RCTs comprising 7108 patients, cetuximab, an EGFR inhibitor, can significantly prolong progression-free survival (PFS) and OS in patients with mCRC in combination with chemotherapeutic agents versus chemotherapy alone (26). In addition, REVERCE was a phase 2 randomized study on the sequential treatment of regorafenib followed by cetuximab compared with cetuximab followed by regorafenib in patients with mCRC (UMIN000011294). The results from this study showed that patients in the regorafenib followed by cetuximab arm had better PFS (PFS: 5.2 vs 1.8 months; HR, Hazard Ratio: 0.29) and OS (17.4 vs 11.6 months; HR: 0.61; P=0.03) than those who received cetuximab before regorafenib (27).”

Comment 6: Please updated their literature research, two recent studies are suggested to be cited: Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study. Eur J Cancer 2019 Dec;123:146-154; Real-world evidence of the safety and effectiveness of regorafenib in Taiwanese patients with metastatic colorectal cancer: CORRELATE Taiwan. J Formos Med Assoc. 2021 Jan 6:S0929-6646(20)30615-X. doi: 10.1016/j.jfma.2020.12.015.

Reply 6: We thank you for the comment, the following paragraph was updated from the prospective observational study and data from Taiwanese cohort was added.

Changes in the text: Page 12 Line 273-280

"Furthermore, findings from CORRELATE, a prospective, observational study showed that 80% of the patients treated with regorafenib had drug-related AEs and 36% suffered from grade ≥3 AEs. The incidence of AEs was relatively lesser compared to other studies, which authors attributed to the fact that almost half of the patients received less than recommended daily dose (160mg/day) of regorafenib (46). The real-world analysis of the CORRELATE trial in the Taiwanese cohort depicted a consistent safety report as observed in Asian patients, in trials such as the CORRECT and the CONCUR studies, suggesting HFSR occurring in 33.59% of patients (47)."

Minor Essential Revisions:

Comment 1: Typo and grammatical error need to be improved by an expert good at English-editing.

Reply 1: Thank you for the comment. The revised manuscript has been copy edited professionally for English language.

Changes in the text: Multiple

Comment 2: A figure indicated the flow chart of the literature search strategy should be provided.

Reply 2: As the study in context is a narrative review, we have not provided the flow chart. However, the search strategy and selection criteria are mentioned in the revised manuscript as per the narrative review checklist.

Changes in the text: None

Comment 3: The quality of the figures should be improved.

Reply 3: Thanks for the comment. The quality of the figure was enhanced and set to 600DPI. The resolution of the figures has been increased.

Changes in the text: None

Reviewer B

The authors have summarized the results of previous studies of regorafenib and fruquintinib.

Following minor aspects are missing that might improve the value of this article.

Major comments

Comment 1: It's redundant overall, so I think it needs to be explained a bit more concisely.

Reply 1:

Thank you for the comment. We acknowledge the fact that regorafenib and fruquintinib were previously compared in meta-analysis and network meta-analysis after systematic review in patients with CRC. However, all the published meta-analysis included only RCT evidence for statistical analysis. While RCT evidence may provide good internal validity, in case of CRC, the patient age group in RCT settings cannot reflect real-world age distribution. Meta-analysis of real-world evidence has not been performed for comparing regorafenib and fruquintinib mainly because of the unavailability of real-world evidence for assessing the effectiveness of fruquintinib. Hence, in this narrative review we have summarized the RCT and real-world evidence for assessing regorafenib and fruquintinib which was not done in previous meta-analysis. Also, the heterogeneity with respect to age in the different RCTs cannot be accounted for satisfactorily in meta-analysis. Further, while the previous studies also included other drugs like TAS-102, the current narrative review, included only fruquintinib and regorafenib since both have similar modes of action. This is of significance since current studies are also evaluating the combination of angiogenic inhibitors and PD-1/PD-L1 inhibitors.

A part of this explanation has been included in the revised manuscript.

Changes in the text: Page 14-15 Line 333-343

"Although previous meta-analyses have compared the efficacy of regorafenib and fruquintinib, they had included only RCT evidence for statistical analysis. Although RCT evidence may provide good internal validity, in case of CRC, the patient age group in RCT settings cannot reflect real-world age distribution. Meta-analysis of real-world evidence has not been

performed for comparing regorafenib and fruquintinib primarily because of the nonavailability of real-world evidence for assessing the effectiveness of fruquintinib. Moreover, the heterogeneity with respect to age in the different RCTs cannot be accounted for satisfactorily in meta-analysis. Further, while previous studies also included other drugs such as TAS-102, the current narrative review included only fruquintinib and regorafenib as both have similar modes of action. This is of significance considering that current studies are also evaluating the combination of angiogenic inhibitors and programmed cell death ligand-1inhibitors."

Minor comments

Comment 1:

a) P2 L22 to 30

Consider removing it as it is verbose and does not contain new insights.

b) P5 L125

The quoted part in citation (36) is strange, so please ad it to the end of the sentence.

c) P5 L146 to L150

Please consider deleting citation (37) as there is no additional information.

d) P8 L225

After 'that', there is only 'o', is it a mistake?

Reply 1: Thank you for your valuable comments, we have revised the manuscript with following changes in the text.

Changes in the text:

a) P2 L22 to 30 was changed to:

"Colorectal cancer (CRC) is the third most prevalent cancer (1,931,590 cases in 2020) and the second leading cause of cancer-related death (935,173 deaths in 2020) worldwide (1). Although it is more common in high-income countries, the rate of its incidence and related mortality is rapidly increasing in many low- and middle-income countries as well (2). The global prevalence of CRC and is higher in men than in women (746,298 vs 614,304) (3). Furthermore, men have significantly higher rates of CRC-

caused mortality compared to women (372,639 vs 320,294), and this difference is observed across all age groups (4). Of all the patients with CRC, metastases are detected in 25% of patients at the time of diagnosis, whereas 50% subsequently advance to metastases which accounts for a higher mortality rate (5).”

b) P5 L125 was changed to:
“Fruquintinib was efficacious in significantly prolonging OS in comparison to placebo (9.3 vs 6.6 months; HR: 0.65; 95%CI: 0.51, 0.83; P<.001) and PFS (3.7 vs 1.8 months; HR: 0.26; 95% CI: 0.21 to 0.34; P<.001). Interestingly, OS did not differ between the treatment arms among patients aged ≥65 years (HR: 0.95; 95% CI: 0.55, 1.63) (39).”
c) P5 L146 to L150, the citation was deleted and added at the end of the sentence:
d) “Moreover, in the randomized, phase IIb study by Xu et al (47), Chinese patients with mCRC received fruquintinib while 24 were given a placebo, in addition to best supportive care. The patients enrolled had received ≥2 lines of prior therapies for mCRC. OS was similar among patients in the fruquintinib arm and those in the placebo arm (HR: 0.71; 0.38, 1.34). However, PFS was significantly better in the fruquintinib arm (HR: 0.30; 95% CI: 0.15, 0.59; *P*<0.001) (40).”
e) P8 L225, “o” after “that” as it was a clerical mistake. The text was changed to:
“Furthermore, findings from CORRELATE, a prospective, observational study showed that 80% of the patients treated with regorafenib had drug-related AEs and 36% suffered from grade ≥3 AEs.”