Author’s response to reviews

Title: Capecitabine plus bevacizumab versus capecitabine in maintenance treatment for untreated characterised KRAS exon 2 wild-type metastatic colorectal cancer: a retrospective analysis in Chinese postmenopausal women

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the comments of the editors and reviewers. Thank you for consideration of our manuscript for publication in your journal. We have reviewed the manuscript according to the reviewers’ comments. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. Based on the comment and request, we have studied comments carefully and have made modification. Below you will find our point-by-point responses to your comments:

Editor Comments:
BMC Gastroenterology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Response: We have already viewed the reports via the online peer review system.

Ridhi Gupta, MD (Reviewer 1):

1. Abstract

What does untreated characterised KRAS exon 2 exactly mean. It is a little unclear so please simplify.

Response: In the "Definitions of the descriptive variables" section, we've defined "untreated": Patients with untreated characterised KRAS exon 2 wt MCC was defined as that patients with characterised KRAS exon 2 wt MCC had failed to undergo radiotherapy, chemotherapy, or surgical resection of colorectal cancer before 6-cycle CAPOXB induction therapy.

2. Conclusion; CAP-B maintenance treatment after 6-cycle CAPOX-B in Chinese postmenopause women with untreated KRAS exon 2 wild-type MCC is poorer tolerated but has a more modest, if any, benefit compared with that of CAP maintenance treatment- can be restructured. Is slightly confusing to the reader. The relevance of post menopausal women with intervention of maintainence treatment is unclear.

Response: Hormone-based therapy is a potential MCC preventive intervention, which is illustrated in the background section. Our aim was to explore this response with anti-EGFR agents in a well-characterized cohort of postmenopausal women diagnosed with KRAS-defined MCC by excluding the hormone as an interfering factor. To our knowledge, these data add to the paucity of existing literature in this area and should serve to inform further investigation of the molecular mechanisms involved in hormone-based MCC chemoprevention.

3. Background.

- Line 28 - 29 : needs reconstruction of the sentence. 2017 data is old data and almost 70% will develop metastatic disease. Please relay data for 2018 or change the tense from 'will develop' to 'did develop'

Response: " did develop " instead of " will develop "

- Please mention how the status of menopause correlates to response with anti-EGFR agents or KRAS wt type MCC
Response: We have added this part in background section: "hormone-based therapy, a potential MCC preventive intervention, may influence carcinogenesis through cellular pathways involving the KRAS oncogene in postmenopausal women. Nevertheless, most existing literature tend to ignore hormones as an interference factor, which is likely to lead to a weakening of the power to draw conclusions."

Using current data from 3 tertiary medical institutions, our aim was to explore this response with anti-EGFR agents in a well-characterized cohort of postmenopausal women diagnosed with KRAS-defined MCC (KRAS exon 2 wild-type MCC) by excluding the hormone as an interfering factor. To our knowledge, these data add to the paucity of existing literature in this area and should serve to inform further investigation of the molecular mechanisms involved in hormone-based MCC chemoprevention.

4. Methods

- First few sentences need reconstruction. Long and difficult to follow. Too many words

Response: "A retrospective study was conducted on Chinese postmenopausal women with untreated characterised KRAS exon 2 wt MCC at 3 tertiary medical institutions from January 2012 to December 2016. MCC was defined by the International Classification of Disease Clinical Modification 10th edition ICD-10 code (C.18–C.20). For these patients, the analysis results of EGFR next-generation sequencing of the RAS/BRAF/PI3KCA genes were available."

Instead of "A retrospective study was conducted on untreated MCC women (defined by the International Classification of Disease Clinical Modification 10th edition ICD-10 code [C.18–C.20]) at 3 tertiary medical institutions from January 2012 to December 2016 for whom the analysis results of EGFR next-generation sequencing of the RAS/BRAF/PI3KCA genes were available."

- Unclear if the patient population were all Kras wt or Kras mutated

Response: In the Methods section, we have already revised the relevant content in revised manuscript.

"A retrospective study was conducted on Chinese postmenopausal women with untreated characterised KRAS exon 2 wt MCC at 3 tertiary medical institutions from January 2012 to December 2016. MCC was defined by the International Classification of Disease Clinical Modification 10th edition ICD-10 code (C.18–C.20). For these patients, the analysis results of EGFR next-generation sequencing of the RAS/BRAF/PI3KCA genes were available. The study cohort included 412 patients diagnosed with untreated characterised KRAS exon 2 wt MCC."

Instead of "A retrospective study was conducted on untreated MCC women (defined by the International Classification of Disease Clinical Modification 10th edition ICD-10 code [C.18–C.20]) at 3 tertiary medical institutions from January 2012 to December 2016 for whom the analysis results of EGFR next-generation sequencing of the RAS/BRAF/PI3KCA genes were available. The study cohort included 412 untreated MCC women."
5. Definitions

- OS: 'from' instead of for any cause (eg page 7 like 2-3)

Response: Done

- How is the tumor content important. Please clarify

Response: The quality of the specimen (tumor cell content), as the core of tissue banks, is closely related to pre-analytical variables.

"The tumour cell content of each sample included, as the core of tissue banks, is closely related to pre-analytical variables and was assessed on haematoxylin–eosin stained slides by an experienced pathologist." instead of "The tumour content of each sample included was assessed on haematoxylin–eosin stained slides by an experienced pathologist."

6. Discussion

- Again not clear of the meaning of untreated Kras exon 2 wt? Does this mean that patients were not treated. If so, these are patients that have received 6 cycles of CapeOxB or FOLFOX B. Please clarify

Response: In the "Definitions of the descriptive variables" section, we've defined "untreated": Patients with untreated characterised KRAS exon 2 wt MCC was defined as that patients with characterised KRAS exon 2 wt MCC had failed to undergo radiotherapy, chemotherapy, or surgical resection of colorectal cancer before 6-cycle CAPOXB induction therapy.

- Page 10 - line 48 - post menopau'sal' not post-menopause

Response: We have already revised the relevant content in revised manuscript.

"postmenopausal" instead of "post-menopause"

- Page 12: line 33-38: this appears to be the conclusion but not sure of what this means, not clear to the reader. Please restructure

Response: We've deleted that sentence: "The current study exhibited that indeed, a CAP strategy that disregards routine use of bevacizumab has no tendency to produce perceptible compromise in either short- or long-term outcomes in postmenopausal women with untreated KRAS exon 2 wt MCC."
- Page 12: line 55: incorrect use of adjuvant or were patients previously treated surgically.

Response: "in the CAP-B setting" instead of " in the adjuvant CAP-B setting". Patients were not previously treated surgically.

7. Conclusion

Please replace poorer for 'poorly' .

Response: Done

Kuan-Chih Chen (Reviewer 2):

1. This retrospective study is conducted for comparing median progression-free survival and median overall survival of untreated characterised KRAS exon 2 wild-type metastatic colorectal cancer in Chinese post-menopause women using therapy with capecitabine plus bevacizumab and capecitabine. The study is well designed, and the manuscript is written comprehensively, however, I think this study is lacking of novelty because 4 previous studies have shown positive results (Alfonso PG, 2013; Alfonso PG, 2012; Amin M, 2015; Bazarbashi S, 2011). The only difference is that this study emphasized on Chinese post-menopause women, however, in your article, the reason is not clearly explained. Would you please give more explanation?.

Response: Postmenopausal hormone therapy, which represents a potential colorectal cancer preventive intervention, may influence carcinogenesis through cellular pathways involving the KRAS oncogene. However, to date, no prior studies have reported associations between postmenopausal hormone therapy and colorectal cancer subtypes stratified by somatic KRAS mutation status. Using current data from 3 tertiary medical institutions, our aim was to explore this response with anti-EGFR agents in a well-characterized cohort of postmenopausal women diagnosed with KRAS-defined MCC(KRAS exon 2 wild-type MCC) by excluding the hormone as an interfering factor. To our knowledge, these data add to the paucity of existing literature in this area and should serve to inform further investigation of the molecular mechanisms involved in hormone-based MCC chemoprevention. Some previous studies have neglected, to some extent, the effects of hormones, or the heterogeneity of subjects.

2. Do you consider to put the statement of lacking of generalisability in the limitation part of your manuscript?

Response: According to your opinions, we have already added the statement of lacking of generalisability in the limitation part.

"our analysis has the lack of generalisability because our study population included only postmenopausal women with KRAS exon 2 wild-type MCC."
3. How do you decide the sample sizes in this study? Do you think the patient number is adequate in each arm?

Response: The sample size is based on the medical condition of 3 tertiary medical institutions, as well as inclusion and exclusion criteria.

Sample size varies greatly among studies, ranging from tens of patients to thousands of patients, even within a meta-analysis investigating the same question. Our knowledge about the influence of trial sample size on treatment effect estimates is based on the small study effect—the tendency for small studies to report greater treatment benefits than large studies in the same meta-analysis. The concept of a single threshold to distinguish small studies from large studies, whatever the medical area or intervention being tested, is not straightforward. For binary outcomes, the required sample size depends on the magnitude of treatment effect as well as the number of events and frequency of the medical condition. Therefore, a study of 100 patients can be considered large for certain medical conditions and small for others.

4. Do you compare underlying disease of these two groups? Because underlying disease may play a role of confounding factor in these two groups.

Response: Underlying disease may play a role of confounding factor in both groups. Our study has certain limitations, such as underlying diseases, that need to be considered in the interpretation of its results. We have already added the statement of underlying diseases in the limitation part. Though our algorithm for identification of patients with KRAS exon 2 wild-type MCC, there still remains a risk of some underlying diseases. However, it is well established that there is no between-group statistical significance in baseline data; a relatively homogenous group of patients with KRAS exon 2 wild-type MCC. We did not examine prescribing patterns in clinical subgroups, such as patients with mild pneumonia, which should be addressed in future work. Because the purpose of this study was to examine recording of diagnosis and therapeutic outcomes only on the premise of baseline data consistency. Variation in underlying diseases within the same therapeutic class were not considered.

5. In table 3, the first letter of "progression-free survival rate" should be capitalized.

Response: We have already revised the relevant content in Table 3.

"Progression-free survival rate" instead of "progression-free survival rate"

6. Do you use STROBE checklist for your study design?

Response: The article was completed according to STROBE checklist.

-------------------Declarations-------------------
> Ethics approval and consent to participate

Done

> Consent to publication

Done

> Availability of data and materials

For all journals, BioMed Central strongly encourages all datasets on which the conclusions of the manuscript rely to be either deposited in publicly available repositories (where available and appropriate) or presented in the main paper or additional supporting files, in machine-readable format (such as spreadsheets rather than PDFs) whenever possible. Please see the list of recommended repositories in our editorial policies.

Done.

> Competing interests

All financial and non-financial competing interests must be declared in this section. See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

The authors declare that they have no competing interests.

> Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Done

> Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Done