

Peer Review File

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Review Comments

Reviewer A

Comment: This is a well written review, and easy to understand. It is a very long paper, and the results section regarding the RAISE study is very comprehensive. Perhaps even a bit too comprehensive as the numerous analyses (papers published) may lead to findings by chance. The authors could perhaps elaborate a bit more on that issue in the discussion section. One may argue though whether a comprehensive and large review is indicated based on three clinical trials, one retrospective and two case reports?

Reply: Thank you for your positive feedback on the manuscript. We agree that the review is lengthy and comprehensive. We feel this is owing to the wealth of data available surrounding the use of ramucirumab in a 2nd-line setting for colorectal cancer.

We recognise that some of the studies conducted are exploratory in nature, and hence associated with limitations. However, although the results of such studies should be treated with caution, we consider that they can provide important information that can be used to identify patient subgroups that will potentially benefit from treatment with ramucirumab, and to indicate areas for further research.

Changes in the text: We have added a paragraph on the possible limitations of such studies to the 'Discussion' (page 13, lines 286–291), and have made a few changes in the 'Introduction' (page 4, lines 66–68), 'Discussion' (page 13, line 266) and 'Conclusion' (page 14, line 302) to emphasise that some of the studies were exploratory only.

Additionally, we have shortened the manuscript slightly, mainly by deleting details in the text that are repeated in the figures. We have made some amendments to the text in the following 'Results' subsections, 'RAS/BRAF mutation status' (page 5, lines 85 and 95; page 6, lines 99–101), 'Time to tumor progression during first-line therapy' (page 6, lines 112–114), 'Advanced age' (page 7, line 122), 'Tumor sidedness' (page 7, lines 128–130), 'Baseline carcinoembryonic antigen levels' (page 7, lines 138–140), and 'Baseline VEGF-D levels' (page 8, lines 154–160).

Reviewer B:

Comment: Well written review. The authors should be commended on the review with all data related to the use of Ramucirumab in 2nd line setting for colorectal cancer in one article.

Reply: We thank you for your kind review of our manuscript.