



Athens, 14th of November 2021

Reviewer 1 (05562085)

General comments to authors: Thank you for this review on a very important topic. The paper is well organized by topic....Overall, it is a nice summary of the evidence.

1. Reviewer's Comment: There are some minor improvements on the grammar and language that would make the paper easier to read, and it should be reviewed once more for those changes. Regarding the content

Authors Reply: The document was revised and language corrections were made according to fine tuning.

2. Reviewer's Comment: On Page 6- you state "thus VEGF inhibits....the pathway" I believe that is meant to read: "thus bevacizumab inhibits" - please verify this. Again, on page 6, you call results of VEGF research "contradictory". But go on to describe several consistencies, in that VEGF seems to be prognostic, but does not necessarily predict response to therapy. This should be clarified.

Authors Reply: The phrase was changed from " thus VEGF inhibits....the pathway" to " thus bevacizumab inhibits the signaling pathway". On page 6 the paragraph "Due to the dominant role of VEGF in angiogenesis, were an independent predictor of recurrence [6, 16]" was changed and replaced by "Due to the dominant... with cytotoxic chemotherapy plus bevacizumab".

3. Reviewer's Comment: In the section on MVD-- you use disease free survival and PFS as one outcome, but they are distinct and that should be clear.

Authors Reply: In the MVD section the phrase "A systematic review and meta-analysis..... with surgery and chemotherapy (21)" and the paragraphs " Since MVD is a biomarker for the quantification of angiogenesis... with the anti-angiogenic agent bevacizumab" and "In 2006, Jubb et al... in mCRC this has not yet been demonstrated" have been added.



Reviewer 2 (05601692)

Comments to authors: Colorectal cancer is one of the most common cancers affecting millions of people around the world. The effective treatment for the metastatic colon cancers includes the use of chemotherapeutic agents targeted against EGFR, B-RAF and angiogenesis. In this review, the authors have reviewed the relevant literature and the recent advances on angiogenesis inhibitors focusing on Bevacizumab, a monoclonal antibody that targets VEGF-A. They also wrote a section on how the microvascular density increases during the progression of adenoma to adenocarcinoma through abnormalities in vasculature, and on how cancer cells enter the blood circulation enhancing tumor metastasis. The section on micro-RNAs which can serve as biomarkers is highly relevant and adds strength to the paper.

1. Reviewer's Comment: Minor comments: My only suggestion is that the authors can briefly expand on the immune-check point inhibitors and their targets in the discussion section.

Authors Reply: In the section THE CROSSTALK BETWEEN ANGIOGENESIS AND IMMUNITY the paragraphs "Immunotherapy is now a key therapeutic weapon in the treatment of many cancers... except in tumors with microsatellite instability (MSI) (57)" and "As the immunosuppressive tumor ...and hepatocellular carcinoma [atezolizumab and bevacizumab] (62) has been added.

In addition the phrase has been added to the CONCLUSIONS: "Finding new molecular targets for different approaches including immunotherapy may enrich treatment options for CRC in the future."