

Dear Editor,

Thank you very much for considering the invited review '**Rationally designed treatment for metastatic colorectal cancer (mCRC): current drug development strategies**' for publication in World Journal of Gastroenterology.

I have addressed the comments of the peer-reviewers in a point-by point discussion:

Reviewer 1:

- 1) GG1: changes have been made accordingly and 'mutant' has been spelled out. A reference to the connection between the MAP-kinase and PI3K-AKT-mTOR pathways and relevant cell surface receptors has been made.
- 2) GG2: The rationale has been given and clarified.
- 3) GG3: changes have been made accordingly.
- 4) GG4: The relationship between MSI and the role of PARP inhibition has been expanded.
- 5) GG5: This paragraph has been omitted due to the limited impact this drug has made in mCRC.

Reviewer 2:

- 1) It is mentioned that the disease is invariably fatal and the only treatment is chemotherapy. It should be briefly acknowledged that a small number of patients can be successfully treated by surgical resection of liver metastases.

These comments have been acknowledged in the manuscript.

- 2) In 2 places on page 3, approval for use of agents is mentioned. Presumably the approval referred to is in the United Kingdom. It is not the same in my country for example. Since this article is for an international audience, the reference to specific approval should be deleted.

These comments have been acknowledged in the manuscript.

- 3) Inactivation of MLH1 protein does not lead to BRAF mutation. The BRAF mutation is present in the benign colorectal polyp from which the cancer arises. The tendency of these tumours to acquire heavy CpG island

methylation (CIMP) leads to methylation and silencing of MLH1 at the time the benign polyp transitions to invasive malignancy. CIMP should be mentioned as background to the discussion to DNA-methylating agents.

CIMP has been mentioned in the context of MSI and potential subgroup selection for DNA- methylating agents.

- 4) Also syndromes should not be plural at the top of page 8. There is only one relevant syndrome (Lynch syndrome)

Corrected.

- 5) The tables should be referenced in the text - the section headings (Mitogen-activated protein kinase (MAPK) pathway, PI3K-AKT-mTOR pathway etc) should be made clearer with different font

Adjusted.

- 6) On page 5, line 6 "where" should be "were" This spelling mistake has been corrected.

Corrected

Reviewer 3:

- 1) An additional figure of the relevant molecular pathways has been added.

Kind regards

Dr Hendrik-Tobias Arkenau