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Title: *Rationally designed treatment for metastatic colorectal cancer (mCRC): Current drug development strategies.*

Authors (typed):

Pavlina Spiliopoulou, Hendrik-Tobias Arkenau

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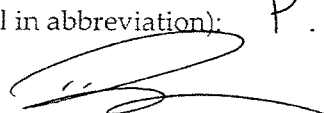
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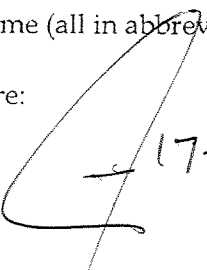
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Format for ANSWERING REVIEWERS



February 15th, 2014

Dear Editor,

Please find enclosed the edited manuscript number 8124 in Word format

Title: Rationally designed treatment for metastatic colorectal cancer (mCRC): current drug development strategies

Authors: Pavlina Spiliopoulou, Hendrik-Tobias Arkenau

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8124

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer

Reviewer 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.
- GG2: The rationale has been given and clarified.
- GG3: changes have been made accordingly.
- GG4: The relationship between MSI and the role of PARP inhibition has been expanded.
- GG5: This paragraph has been omitted due to the limited impact this drug has made in mCRC.

Reviewer 2:

- "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.

- "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.

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

Corrected accordingly

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

Reviewer 3:

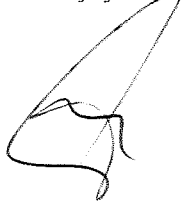
- A figure with the relevant molecular pathway was created and added.

3. References and typesetting were corrected

4. Changes as suggested by the Editor have been made

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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