PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79980

Title: Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: Updates and beyond

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03270754

Position: Editorial Board

Academic degree: MD, PharmD, PhD

Professional title: Assistant Professor, Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Lebanon

Manuscript submission date: 2022-09-13

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-14 01:27

Reviewer performed review: 2022-09-14 06:54

Review time: 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1. The manuscript focus on Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: updates and beyond, after checked the references in Pubmed, many references focus on drug-resistance in CRC including review artices such as Drug resistance and new therapies in colorectal cancer. Van der Jeught K, Xu HC, Li YJ, Lu XB, Ji G.World J Gastroenterol. 2018 Sep 14;24(34):3834-3848. doi: 10.3748/wjg.v24.i34.3834. . 2. This topic focus on drug resistance Molecular mechanisms and metasis, but the article consisted with RESISTANCE TO THERAPY Or TARGETED THERAPYor BEATING RESISTANCE TO TARGETED THERAPY，very strange？ 3. The structure of the article was confused, I think firstly introduce the targeted therapy and drug resistance phenomenon, then discuss the possible mechanisms such as Cancer stem cells，Tumor microenvironment。。。then disucuss beating resistance strategy. 4.The manusrcipt foucus on mechanisms, but so many words introduce the targeted therapy, so please highlight the mechanisms part. 5. The mechanisms of drug -resistance I hope add a Figure, this is very important . 6. The English need much more polish.

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Manuscript NO: 79980

Title: Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: Updates and beyond

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05391966

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Lebanon

Manuscript submission date: 2022-09-13

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-17 03:25

Reviewer performed review: 2022-09-17 04:07

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript could be accepted.

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Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79980

Title: Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: Updates and beyond

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06272301

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor, Associate Research Scientist

Reviewer's Country/Territory: China

Author's Country/Territory: Lebanon

Manuscript submission date: 2022-09-13

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-13 10:30

Reviewer performed review: 2022-09-22 01:45

Review time: 8 Days and 15 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This review is well-written and easy to understand. The authors reviewed in detail the mechanisms of resistance to conventional therapies for mCRC, discussed the molecular mechanisms and efficacy of new targeted therapies, and further discussed the problems and solutions of resistance to these targeted drugs. This article summarizes the results of a large number of clinical trials, with sufficient demonstration and clear logic, which meets the requirements of this journal. I recommend that the manuscript should be accepted. However, there are several minor problems in the article, which can be further optimized: 1. The author lists many tables to summarize the targeted drugs in the paper, but only one figure describes the targeted drugs. Considering that traditional drug resistance mechanisms, targeted drug resistance, and solution strategies are also very important components of the article, I suggest that several additional summary figures can be drawn based on these contents to facilitate readers' understanding and reading.   2. In the last part of the article, the author emphasizes the importance of implementing better preclinical models for research, but this part is not explicitly mentioned in the abstract and introduction, which is slightly out of place.   3. In the end, the author can elaborate on his understanding of "personalized" treatment of CRC and optimization of existing targeted therapy strategies (such as drug combination) in more detail, and summarize some meaningful suggestions or opinions to show his unique insights.   4. In addition, there are some grammatical problems and formatting problems in the manuscript (such as the space before paragraphs), which need to be carefully considered by the author and modified. Some of the possible inappropriacies are listed below. I hope the author can review the whole paper carefully. (1) Please check the

spelling of "5-flourouracil (5-FU)" in the third paragraph of the introduction. (2) Please check the verb "has" in the sentence " New drugs whose action is directed at specific pathways implicated in CRC pathogenesis, including the epidermal growth factor (EGFR) pathway, has been tested in preclinical models and in clinical trials. " in the fifth paragraph of the introduction. (3) Please check the "leading" in the first sentence in the "Tumor Microenvironment" section for grammatical errors. And please check if "mediates" is correct in the sentence "During tumor formation, interactions between tumor and stromal cells and secretion of soluble inflammatory molecules mediates the attraction of the above-mentioned cells, which goth tumor cell survival and metastasis.". Please check for any ambiguity before and after the sentence "One of the most important components of tumor stroma are TAMs and CAFs." (4) Please check the use of "include" in the penultimate sentence and "have" in the last sentence of the "Gut microbiota" section for mistakes. (5) Check whether the phrase "Adverse events rates" in the last sentence of the fourth paragraph Targeting EGFR is wrong. (6) Please check whether the phrase "is implicate" in the last sentence of the first paragraph Targeting HER is wrong. Please check the correct noun form of "subgroup" in the sentence " Several factors may account for this variability, including small sample size, different antibodies used for immunohistochemistry (IHC), and analysis of different subgroup of patients with multiple clinical characteristics." in paragraph 2. Please check whether there is an extra "the combination of" in the sentence " HER2 amplification was detected in clinically unresponsive KRAS WT patients, and the combination of the combination of lapatinib (a dual EGFR/HER2 tyrosine kinase inhibitor) and pertuzumab induced an increase in response rate and tumor regression, in agreement with clinical studies in patients with similar clinicopathological characteristics." in the second paragraph. (7) Consider whether "table" in the article should be "Table". (8) In the part of "MEK and Mutant BRAF," please consider whether "are" should be changed to "is" in the last sentence "

BRAF, along with RAS, are the only available biomarkers for advanced CRC that are used in   clinical practice." of the first paragraph considering" along with ". (9) Please check the use of "were" in the penultimate sentence of the "Immune checkpoint inhibitors".