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Targeting Enhancer of Zeste Homolog 2 as a promising strategy for cancer treatment

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Dear Editor:

First of all, please thank the reviewers for their thoughtful suggestions. We modified the manuscript as follows based on their recommendations.

Reviewer #1

"The manuscript would benefit of a comprehensive table listing all the different targeting strategies and the corresponding level of development (in vitro, phase 1, 2 etc)"

We prepared a table where we summarized, for each EZH2 inhibitor described in the manuscript, the mechanism of action and the level of development.

"as well as a small separate description of the most important results of these studies"

We have described in details the results of EZH2 inhibition studies.

Reviewer #2

"In my opinion, the main drawback of the whole paper derives from the misleading use of inhibition (lack of activity) in contexts where an interaction is precluded, which may or may not mean loss of activity. Therefore, a revision of the whole text for clarification is required."

EZH2 dependent H3K27 tri-methylation is strictly related to the formation of PRC2 complex; if a drug destroys the binding between EZH2 with other subunits of the complex, it inhibits its activity

"Figure 1 The figure is poorly explained in the legend"

The original figure legend has ben updated with a clearer and more detailed version.

"The meaning of the dashed lines is not mentioned..... residues shown at the nucleosome"

We prepared a new figure and described in the legend symbols and images.

Minor points in Abstract and Section 4.4

We corrected the errors and rephrased the indicated sentences more clearly

Reviewer #3

"The final chapter (conclusions) should clearly list the most promising developments and future perspectives without going in too much detail. Question of interest are: Are there still questions that need to answered regarding EZH2 and the PRC2 complex? How well defined is EZH2 ' role in cancer? Is it sensible to target such an important molecule that fulfills crucial roles in development? What kind of adverse effects can be expected?"

More details were added to the conclusions in order to list the most promising developments.

"*It is informative to more elaborately discuss the composition of the PRC2 complex after all this is the context in which EZH2 operates*"

We described PRC2 complex in Section 2.

"*One cannot say that the miRNAs listed here let7a-d, miR-26a, miR-101, miR-146a, miR-200b,c are tumor-suppressive miRNAs this totally depends on cancer type and context* "

We remove "tumor-suppressive" from the sentence.

"Abstract, line 12 – Note that the manuscript is a review not a commentary"

The manuscript is an editorial; we changed "commentary" with "editorial".

"Abstract, line 16 – "Moreover, mutations of these proteins…." What do the authors mean? Which proteins are meant in this sentence? Please clarify"

The sentence has been rewritten.

"Page 7, line 4 – 7 – "Furthermore, the recruitment…….tissue specific differences of EZH2 activity."

It is unclear what the authors try to convey here. Please rephrase"

We rephrased the sentence.

"Page 8, line 1-2 – One reads "…., in fact several studies reported that it is also able to methylate other proteins" Unfortunately references are missing"

Corrected references have been added.

"Page 15, line 8-9 – "…resistance of cancer cells often associated to the treatment with the only chemotherapeutic agents". What is meant here? Please rephrase"

We rephrased the sentence to make it more understandable.

General comment

An English native speaker has reviewed our manuscript.

Regretfully, we cannot provide a decomposable graph in "PowerPoint" or "Excel" since it was created with software named "keynote" (available upon request).

I sincerely hope that after making the suggested revisions you will find the manuscript to be of adequate quality for publication in World Journal of Clinical Oncology

I look forward to hearing back from you and I thank you in advance for your consideration.

Sincerely,

Luigi Marco Bagella