

May/12/2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (9473-edited).

Title: Overcoming endocrine resistance in metastatic breast cancer: current evidence and future directions

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Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 9473

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

1 Title has been shorten to 12 words

2 Authors' contributions have been enclosed

3 A first reviewer suggested:

1. *In the part of "PUTATIVE MECHANISMS OF ENDOCRINE RESISTANCE", as an important part of the manuscript, the pathways of estrogen receptor modulates gene expression should be classified into different paragraphs which have their own title in each part.*
2. *In the part of "OVERCOMING ENDOCRINE RESISTANCE", the author raised a variety of treatments in HR-positive MBC but had no significant connection with the mechanisms of endocrine resistance above. The author should make some evaluation about the potential mechanism in each treatment to improve the problem.*
3. *If the author could provide more figures about the molecular mechanisms of endocrine resistance, it would be better for our understanding of the study.*
4. *The grammar, spelling and conciseness of the language need improvements.*

A second reviewer suggested:

1. *The introduction to biological grounds of resistance to hormonal therapy in breast cancer would be oversimplified on the expense of thoroughness and clarity.*
2. *The writing style, apart from minor grammatical mistakes, may sometimes lack the logic flow and the scientific wording of statements that should convey the accurate message without confusion, for example possible subjective bias.*
3. *The ultimate goal of the topic is assumed to elucidate and clarify the potential and direction of current research to tailor individualized treatment to breast cancer patients and especially those with resistance to endocrine therapy. The authors should have stressed on such concept through the different parts of the manuscript.*

Revision has been made accordingly. In particular:

1. We reviewed the introductory chapter regarding the mechanism of action of estrogen receptor and putative mechanisms of endocrine resistance, providing

more detailed discussion on the biology of ER and mechanisms of resistance to endocrine therapy (as suggested by the second reviewer, point 1); we discussed the pathways of activation of ER, dividing the discussion into different paragraphs, which have their own titles (as suggested by the first reviewer point 1). We therefore renamed this chapter “biology of estrogen receptor”.

2. As suggested by the first reviewer (point 2) and by the second reviewer (point 3) we clarified and stressed in each part of the paper the connection between possible mechanisms of resistance described in the specific paragraph and possible overcoming. We have modified most of the introductions to each strategy (combining blockade of tyrosine kinase and ER, combining blockade of mTor and ER and multiple blockade of ER) in order to facilitate the reader to understand the connection between mechanism of action and possible strategy to overcome it.
3. As prompted by the second reviewer (point 2) we have modified through the paper some sentences and paragraphs that could generate confusion to the reader and in order to better convey the messages of the review and favoring clarity and scientific accuracy
4. As recommended by the first reviewer (point 3) we added a figure (figure 1, Biology of endocrine receptor) in which we summarize the different pathways of gene regulation of ER and the key mechanisms of resistance that we more extensively explain in the text.

4 The manuscript has been comprehensively edited by a native English speaker and we are now confident that the manuscript attains the 'Grade A' level requested by the journal

5 Figures were provided in editable .PPT format. Legends have been modified accordingly to reviewers' suggestions and to the suggested format.

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

Sincerely yours,

Giorgio Valabrega, MD



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