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To the editor in chief of World Journal of Clinical Oncology

Dear Editor,

We are pleased to submit to **World Journal of Clinical Oncology a revised version of** our manuscript entitled: "**Resistance to targeted therapies in breast cancer**" by Viviana Masoud and Gilles Pagès.

We appreciated the reviewers' and editors' evaluation, and hope that the corrections will meet the approval criteria of the journal.

You will find enclosed a point by point answer to the different concerns raised by the reviewer

We hope that this revised version will be favorably considered for publication in **World Journal of Clinical Oncology,** and we look forward to hearing from you.

Yours sincerely,

Dr Gilles Pagès

Answers to the reviewers:

Reviewer 1 : Grade A (excellent)/Priority publishing/High priority for publication
A nice review. It would be better to provide several figures to illustrate the resistance-associated pathways described in the text, which will greatly help readers and also increase citations.

We thank the reviewer for her/his nice comment. According to her/his suggestion we included two new figures to illustrate our paper. We have also added several new references (the number of references is now more than twice the initial number). We hope that these modifications will convince reviewer 1.

Reviewer 2: Grade C (Good)/Minor language revision/Major revision
The authors reviewed and summarized drug resistance of current breast cancer therapy. The manuscript primarily focus on the potential resistance mechanisms of breast cancer cells cultured in vitro, based on targeting breast cancer cells expressing growth factor receptors (e.g. EGFR, HER2).
For broad interest of readers, relatively detailed info of clinical trials treated in different subtypes and stages of breast cancer should be provided. Such data shown in a table would be more informative, if any.
We thank the reviewer for this very interesting remark. We have now included three tables showing the current therapies used for specific breast cancers and current clinical trials (from phase I to phase III) for future treatments. A specific table (Table 2) is dedicated to the currently investigated treatments targeting the immune system that have given promising results.

In addition, the paper at the end also needs a short section of the future challenges.
A specific section has been included according to this very interesting suggestion.

A precise percent of triple negative breast cancer population must be added prior to about 85% of breast tumor (p17), clarifying this rare specific type and avoiding confusion.
The reviewer was right. The sentence was insufficiently clear. We modified to "*Triple negative breast cancers (TNBC) represent 10-20% of invasive breast cancers in the general population and have been associated with the African-American ethnic group where a clear prevalence of the disease affects up to 28% of all patients within that group*[109]" and we have added a reference (109).

The rationale for using anti-angiogenic therapy (e.g. sunitinib p18) in triple negative breast cancer was missing.
This is a very interesting remark. We have included a paragraph and reference for the rationale of using sunitinib in TNBC as the following: "*Sunitinib seems to suppress angiogenesis, tumor proliferation, migration and growth of basal like breast cancer cells; xenograft models indicate that tumor volumes decrease under sunitinib action but due to its effects on the Notch-1 protein expression and hypoxia through HIF-1, there was an increase in proliferation of breast cancer stem cells. The use of a γ-secretase inhibitor in addition to sunitinib may represent a promising treatment option for TNBC while simultaneously targeting cancer stem cells and angiogenesis*[112].
Sunitinib may prove to be an effective treatment choice for patients with TNBC as this breast cancer subtype may express increased levels of vascular endothelial growth factors (VEGF). High levels of vascular endothelial growth factors (VEGF) may act as a potential prognostic factor in TNBC as the vascular pathway is a key component when targeting this particularly rare subtype of breast cancer[113]."

A few grammatical errors must be corrected, such as adding "of" following one p6, "," following breast p11 etc.
They have been corrected.

Reviewer 3: Grade B (Very good)/Minor language polishing/Minor revision
This is a well-written review about recent developments in targeted therapies of breast cancer. This review covers what it promises to. The authors do a solid job of explaining the basics of breast cancer-targeted therapies. Along with the addition of the resistance in breast cancer-targeted therapies, the authors provide a good resource for readers who are more unfamiliar with resistance mechanisms but also provide detail.
We thank the reviewer for these very positive comments.

Minor concerns: 1. Brief diagrams or drawings on the action and resistance mechanisms of the targeted therapies are helpful.

We thank the reviewer for this comment that will improve our manuscript. We have included two figures to address this concern.

2. An overall breast cancer-targeted therapies is needed.
We thank the reviewer for this comment. We have included a table summarizing the current treatments (Table1). We have also added two tables showing the ongoing clinical trials.

3. Breast cancer combination therapy is a future direction in the field. The authors may strength this discussion.
We thank the reviewer for this comment. We have added a specific paragraph that address the future directions for the treatments and as stated before a specific table for the ongoing clinical trials testing combined treatments and a specific table on clinical trials with molecule targeting the immune system.

Reviewer 4: Grade D (Fair)/Minor language polishing/Major revision
The MS was to make a general overview of the current knowledge in the field of the mechanisms of resistance to targeted therapies in breast cancer. 1. The MS was well written.
We thank the reviewer for her/his kind comment.

However, the mechanisms presented in this manuscript were too simple. 2.The indications of each targeted therapy was not described, and they are very important.
The reviewer is right. We were insufficiently clear on many points and we thank her/him for raising this concern and finally to improve our manuscript. We have more carefully described the current treatments for specific tumor types and we have included a specific table for this purpose (Table 1). We have included two tables that specify the treatments that are currently tested in different phase I to phase III clinical trials. We have also included two figures to address the mechanisms of resistance. We hope that these modifications will definitely convince reviewer 4 who was the less positive.