Author's response to reviews

Title: Decreased Hsp90 expression in infiltrative lobular carcinoma: an immunohistochemical study.

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Author's response to reviews: see over
Dear Editor,

I am sending for publication to your distinguished Journal the revised manuscript entitled: “Decreased Hsp90 expression in the continuum of breast lobular lesions”.

We have made all the revisions indicated by your distinguished Reviewers and have coloured them in RED throughout the manuscript. Please find a point-to-point reply in the next pages.

Yours sincerely,

George C. Zografos,
Professor of Surgery
University of Athens
Reviewer: Shiwu Zhang
“Reviewer's report:
The authors had revised the paper according to the suggestions from the reviews thoroughly. In a word, the paper has potential interesting of clinical significance. I have not furthermore comments about the paper.
Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.”
-We would like to thank you for the encouraging comments regarding the acceptance of our manuscript.

Reviewer: Gulisa Turashvili
“Reviewer's report:
This study has obvious limitations and it is good that the authors address these limitations in the Discussion.”
-We would like to thank you for your thoughtful comments. All your remarks, including those pertaining to the limitations of the study, have been included in the revised manuscript. We believe that the manuscript has been significantly improved after the incorporation of your valuable comments.

“Major Essential Revisions
1. Consider adding a table showing how many normal TDLU, LN and ILC samples had Allred scores 0 to 8. It should also be clarified in Methods or Table 1 that Allred score = %positive + staining intensity.”
-We would like to thank you for this thoughtful comment. A new Table (Table 4) has been added, presenting the detailed results of Allred score in TDLU and ILC. Please note that all information pertaining to LN has been eliminated from the manuscript according to the comments by Reviewer #2 and the Editor.

“2. Dako Envision kit is NOT an avidin-biotin based detection system. Envision systems are based on dextran polymer technology and they are completely avidin-biotin free.”
-We would like to thank you for this careful remark; we would like to apologize for this typographic inadvertence.

“3. In the Discussion section, the authors state: ‘...given that c-erbB2 is positively associated with Hsp90 expression [7], it is tempting to speculate that downregulation of Hsp90 in ILC may be a c-erbB2 related event’. This speculation is based on Pick et al. paper as no association was observed between Hsp90 Allred score and c-erbB2 status in ILC subgroup. There are only 7 HER2+ positive ILC patients in this cohort which may be one of the reasons for this lack of association between HER2 and Hsp90. This needs to be clarified in the same paragraph.”
-We would like to thank you for this extremely insightful comment. The respective comment pertaining to the seven c-erbB2 positive patients has been added (Discussion, paragraph 3, lines 4-8).

“4. Nuclear expression of Hsp90 in <5% cells may be caused by technical reasons and this should be commented.”
We would like to thank you for this valuable remark, which has been added in the revised manuscript (Discussion, paragraph 6, lines 3-4)

“Minor Compulsory Revisions
1. Fig. 1a: hematoxylin is more violet as opposed to blue in Fig. 2a.
2. Figure size needs some formatting.”
-We would like to thank you for these comments. Please note that Figure 2 has been eliminated from the revised manuscript, as it pertained to LN. Concerning Figure size, both Figures 1 and 3 have been formatted so as to contain symmetrical figure parts.

“Discretionary Revisions
None
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests”
-Once again, we would like to thank you for your thoughtful comments, which have led to substantial improvement in our manuscript.

Reviewer: Matthew H Herynk
“Reviewer's report:
In this revised manuscript the authors have adequately answered the points raised with the exception of Major compulsory revisions #1 and #2.
1) In vitro mechanistic studies have not been done and the authors have revised the manuscript to report "in vitro mechanistic studies seem indispensable for definitive conclusions." If these studies are "indispensable" as the authors report they need to be done. Additionally the authors state "the inability to perform such studies in the clinical setting..." An inability to perform in vitro mechanistic studies (western blotting as suggested by the authors would be a confirmation of their findings and not be a mechanistic study) in their current clinical setting would require a collaborative effort and significantly increase the importance of this manuscript and is more important in light of #2 (see below).”
-We would like to thank you for this important remark. We have acknowledged the need for mechanistic studies and we believe that, through your remarks, we have provided the audience with a sincere, objective and dialectical presentation of the study limitations. Following this comment, we have also added a brief comment on the need for future collaborative efforts which unfortunately have not been feasible at present (Discussion, paragraph 8, last two lines).

“2) The authors are correct that the total sample size has been increased from 44 to 97. However the samples are divided into LN and ILC sets. Forty-four of the 65 LN samples have been previously reported and a 50% increase in LN samples does not warrant republication of the data. The LN sample size should be significantly increased allowing the authors to draw definitive conclusions or withdrawn from this manuscript as the small increase in LN sample size does not elevate scientific knowledge. The 32 ILC case are new data and do warrant publication.”
We would like to thank you for this extremely important comment. Although our Center represents a Referral Center of preinvasive lesions in Greece, there was no possibility for us to further increase the sample size of LN cases not coexisting with other lesions. As a result, we had to withdraw all information concerning LN. Please note that this results in the modification of the title, as well as merging of Tables 2 and 3.

“Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.”

-Once again, we would like to thank you for your thoughtful comments, which have led to substantial improvement in our manuscript.