**Author’s response to reviews**

**Title:** Adjuvant chemotherapy could not bring survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 invasive lobular carcinoma of the breast: a propensity score matching study based on SEER database

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**Version:** 2 **Date:** 23 Dec 2019

**Author’s response to reviews:**

Dear Renaud Sabatier,

BCAN-D-19-02948R1

Adjuvant chemotherapy could not bring survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 invasive lobular carcinoma of the breast: a propensity score matching study based on SEER database

Thank you for consideration of our manuscript for publication in your journal. I’m very appreciate for your comments and suggestions. We have revised and polished the manuscript according to reviewers’ comments.
I’m writing this letter to provide a point-by-point response to your and two reviewers’ points raised. All changes to the manuscript are indicated in the text by highlighting.

Editor Comments:

After revision, I suggest to add the following comments to those made by the two reviewers.

1. There is no details about endocrine therapy, which is the essential adjuvant systemic treatment for patients with ILC.

Answer: SEER database actually didn't provide the information of patients' endocrine therapy. The endocrine therapy is the essential adjuvant systemic and also the undisputed standard of treatment for ILC patients with hormone receptor positive. And therefore we have good reason to believe that the ILC patients with hormone receptor positive in SEER database were given endocrine treatment following common guidance. We had considered this limitation of our study and mentioned in the manuscript (in line 4 paragraph 8 of discussion section).

2. The chemotherapy record in SEER database is classified as "No/Unknown" and "Yes". Actually, we don't know whether the patients recorded as "No/Unknown" actually received chemotherapy.

Answer: This is indeed an important deficiency for the SEER database to address our question. We have added this limitation of our discussion section (in line 6 paragraph 8 of discussion section). So far, there are no clinical trials involving more than one thousand such patients with definite chemotherapy except for the public database. Therefore, our study still has great enlightenment for the adjuvant treatment of low/median-risk ILC with HR+.

3. The authors should exclude all cases with SBR grade 4 of the PSM analysis.

Answer: The editor is correct. The rare SBR grade 4 sample in the original sample would cause the bias of PSM. We have excluded all cases with SBR grade 4 at the time of patient enrollment (table1,2,3) (figure1). We also found that the natural death of the patients who were older than 80 years old would affect the results of survival analysis. At the same time, patients older than 80 are contraindications to chemotherapy. We have excluded all cases older than 80 years old at enrollment and revised the results section of our manuscript (table1,2,3) (figure1,2,4). In order to make the expression of the results consistent with the title of the manuscript, we changed the tumor size to the classification variable of T stage (T1b/T1c), and changed the age to the classification variable.
4. (Dear editor, you did not give us this term.)

5. The authors should provide more information with respect to the variable included in the cox proportional hazard model and in the propensity score model. It is quite difficult to understand why the authors reused a cox model in the PSM population given the kernel distribution.

Answer: We have provided the information with respect to the variable included in the cox proportional hazard model and in the propensity score model (Table3 and figure 1). For the variables included in the PSM analysis, to estimate the PS score, we used the Logit model with the following steps. We start with estimating probabilities using the Logit model, then evaluating the Effects of Chemotherapy using PSM (We used command “psmatch2” in Stata). We also provide the dofile of Stata as supplementary material in this version of our manuscript. We reused a cox model in the PSM population in order to obtain more precise results of multivariate analysis and verify with the results of original samples.

6. English editing seems necessary to ensure that an international audience can clearly understand the text. It seems to me that there is a confusion between breast cancer mortality and breast cancer specific survival in results and discussion sections. I would encourage the authors to carefully proofread the manuscript.

Answer: SEER database provides the data of breast cancer specific mortality and overall survival. In order to make international audiences understand the text clearly, we described the HR for overall survival in multivariate Cox models in our manuscript. We have rewritten the result section and table3.

Reviewer reports:

Megan Kruse (Reviewer 1): I think that is a very important study for the ILC community. The propensity score matching is a nice technique that I have not seen used in other similar studies. I would consider moving much of the information regarding E-cadherin mutations and Oncotype Dx testing to the introduction/background section as it does not seem to fit well in the discussion as rationale for the results.
Answer: We rephrase the information regarding E-cadherin and molecular atlas (maybe Reviewer 1 termed it Oncotype Dx testing) in line 5 paragraph 1 of background section, to make it seems to fit well in the discussion. We rephrased as “This distinctive feature of classical ILC results from the E-cadherin loss on tumor cell membranes [3,4]. Importantly, loss of E-cadherin not only results in a dysfunctional E-cadherin-catenin complex with consequences on cell-cell adhesion but also the different inter-cellular and intracellular signaling pathways [5].”

I would also consider rephrasing the main conclusion as "In this study, adjuvant chemotherapy did not improve survival for patients with HR-positive, HER2-negative pT1b-cN0-1M0 ILC”. The "could bring no survival benefit" is somewhat confusing. Also, I would consider removing the "contribute to BCSM" as you previously stated that you do not think that the difference in BCSM is related to chemo but rather patient based characteristics.

Answer: We totally agree with the opinion of Reviewer 1 concerning the main conclusion in Abstract. We rephrase the main conclusion as “In this study, adjuvant chemotherapy did not improve survival for patients with HR-positive, HER2-negative pT1b-c/N0-1/M0 ILC.”

(conclusion section in Abstract)

There is odd punctuation at the end of the second paragraph in the background section that confuses the meaning of the paragraph that should be rephrased- the current sentence reads "Thus, if adjuvant chemotherapy is ineffective for relatively early stage patients with HR-positive, HER2-negative ILC? Hereunder this issue is not yet settled in published clinical studies”

Answer: We rephrase the current sentence as “So for it is not yet settled in published clinical studies that whether adjuvant chemotherapy is effective for relatively early stage patients with HR-positive, HER2-negative ILC.” (in line 5 paragraph 2 of background section)

A similar grammatical issue is present at the beginning of the 4th paragraph in this section that states " In a dilemma, for HR-positive, HER2-negative pT1a/N0-1/M0 ILC...". I would also be careful making the assumption that all pT2N0-1 ILC patients receive chemotherapy and endocrine therapy as this does not seem consistent with clinical practice in the US.

Answer: This sentence is easy to misunderstand, so we avoid of talking about the HR-positive, HER2-negative pT1a/N0-1/M0 ILC or pT2/N0-1/M0 ILC. We rephrase the current sentence as “ In a dilemma, how should we make a treatment choice for HR-positive, HER2-negative, pT1-2/N0-1/M0 ILC, especially, the pT1b-c/N0-1/M0 ILC? (in line 1 paragraph 4 of background section)
Alexandre de Nonneville (Reviewer 2): Hu et al. conducted a SEER database analysis aiming to evaluate the impact of adjuvant chemotherapy in hormone receptor positive, HER2 negative pT1b-c/N0-1/M0 invasive lobular carcinoma.

The authors performed several approaches to adjust baseline differences between groups and to reduce the impact of treatment selection bias, including multivariate Cox model and propensity-score matching.

Unfortunately, the absence of information about endocrine therapy in the SEER database is a major issue here, considering the population of interest (luminal stage I breast cancer).

Answer: The endocrine therapy is the essential adjuvant systemic and also the undisputed standard of treatment for patients with ILC. And therefore we have good reason to believe that the ILC patients with HR+ in SEER database were given endocrine treatment following common guidance. In fact, we had also considered this limitation of our study (in line 4 paragraph 8 of discussion section).