

## **Reviewer #1**

**The authors have put together an excellent paper that is a mix of solid basic science with a clinical correlation. My only slight concern is the number of patients who were censored because they died of 'other causes' it is not made clear how many of these patients existed. There is a huge amount of data presented which makes the paper long and complex. It would almost be better to have two separate papers but published next to one another, however the data presented is very worthy of publication.**

We thank the reviewer for the positive comments and encouragements to advance our work. The number of patients who were censored because they died of “other causes” was shown in Figure 2D, but we forgot to add the legend of the figure, which has been revised in the updated manuscript. Thank you very much.

## **Reviewer 2**

### **Major comments:**

- 1. The paper needs to be revised by an English mother tongue expert.**

Thank you. The paper has been revised by an English mother tongue expert.

- 2. In Material and Methods section the technique of lentivirus transfection must be better explained and the technique of ZEB1 knockdown must be included. Moreover it has to be elucidated if the wound healing assay was conducted in complete medium or in medium deprived of serum.**

Thank the reviewer for these comments. The technique of lentivirus transfection has been better explained in Line 8-15, Paragraph 6 of the “Material and Methods” section in the updated manuscript, and the technique of ZEB1 knockdown has also been included in Line 1, Paragraph 7 of the “Material and Methods” section.

The wound healing assay was conducted in medium deprived of serum, which has been elucidated in Line 1, Paragraph 8 of the “Material and Methods” section in the revised article.

- 3. In the results section, in the first paragraph, (line 9), the CULA4 IHC score values should be inverted .**

Thank you. The CUL4A IHC score values have been inverted in Line 9, Paragraph 1 of the “Results” section in the revised paper.

- 4. In the results section, in the second paragraph, the authors describes the cutoff scores of OS and PFS for high CULA4 expression but figure 2 doesn't show these values that must be added.**

Thank the reviewer for this suggestion. The statistical analysis of the cutoff scores of OS and PFS for high CUL4A expression was performed by using SPSS 19.0 software (SPSS, Inc., Chicago, IL). And it may be easier to evaluate significance of the cutoff scores if they could be showed on the curves. However, SPSS 19.0 software could not facilitate this aim. Thus, the cutoff scores are usually not showed on the curves as presented in published literatures.<sup>[1, 2]</sup>

- 5. In the results section, in the third paragraph, the table mentioned (table 2) must be better explained expecially for HR and CI. In the same paragraph the number of the figures reported is wrong.**

Thank the reviewer for these comments. The HR and CI of the risk factors for overall survival and progression-free survival have been better explained in the third paragraph of the “Results” section in the revised manuscript. And the number of the figures has also been corrected.

- 6. In the results section, in the fifth paragraph, the authors describe experiments conducted in QBC939 cells depleted of CULA4 and in**

**FRH0201 cells overexpressing CULA4 . The authors should also add results conducted in FRH0201 cells depleted of CULA4 and QBC939 cells overexpressing CULA4.**

Thank the reviewer for this professional suggestion. The results conducted in FRH0201 cells depleted of CULA4 and QBC939 cells overexpressing CULA4 have been added in the updated manuscript.

- 7. In the discussion section the authors should also discuss the results obtained for vimentin expression.**

Thank the reviewer for this comment. The discussion about the results obtained for Vimentin expression has been added in Line 16-21, Paragraph 2 of the revised manuscript.

**Minor comments:**

- 1. Reference 6 in the introduction is wrong.**

Thank you for pointing out this mistake. The reference has been corrected.

- 2. In the results section, in the third paragraph, “Moreover high CULA4 expression was correlated with PFS in PHCC patients “ must be changed in “Moreover high CULA4 expression was correlated with lower PFS in PHCC patients “.**

Thank you for this comment. Corresponding change has been made in the updated manuscript.

- 3. In the results section, in the fourth paragraph, (Fig 3B down) must be added to the description of the Matrigel assay.**

Thank you very much. (Fig 3B down) has been added to the description of the Matrigel assay.

- 4. In the results section, in the sixth paragraph, punctuation must to be**

**checked.**

Thank the reviewer for this suggestion. The punctuation has been checked and revised in the updated manuscript.

## **Reference**

- 1 Khoshnoud MR, Lofdahl B, Fohlin H, Fornander T, Stal O, Skoog L, Bergh J, Nordenskjold B. Immunohistochemistry compared to cytosol assays for determination of estrogen receptor and prediction of the long-term effect of adjuvant tamoxifen. *Breast cancer research and treatment* 2011; 126(2): 421-430 [PMID: 20957430 DOI: 10.1007/s10549-010-1202-7]
- 2 Zhou W, Yue C, Deng J, Hu R, Xu J, Feng L, Lan Q, Zhang W, Ji D, Wu J, Liu Q, Liu A. Autophagic protein Beclin 1 serves as an independent positive prognostic biomarker for non-small cell lung cancer. *PloS one* 2013; 8(11): e80338 [PMID: 24260370 PMCID: 3829868 DOI: 10.1371/journal.pone.0080338]