Reviewer’s report

Title: A new mouse model to study the role of ectopic Nanos3 expression in cancer

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Reviewer: Elsa Sánchez-López

Reviewer’s report:

In the current study, the authors reported a new mouse model based on the ectopic expression of Nanos3, a protein that has been found upregulated in many cancers. The authors have generated a conditional-tissue-specific mouse model for Nanos3 overexpression. They have examined the role of Nanos3 in lung tumorigenesis by crossing human Nanos3 transgenic mice with a known model of NSCLC based on the activation of KRAS and the deficiency in TP53 gene. The authors have found that expression of Nanos3 in the lung, increases bronchiolar dysplasia and has a negative effect on female survival.

Major comments:

- In general, this work basically describes the phenotype observed in NSCLC mouse model that express Nanos3 in the lung, so the data shown in Supplementary figure 4 demonstrating the expression of Nanos3 in the NSCLC lung should be shown in the main figures.

- The effect the authors observed in female mice survival upon Nanos3 expression in the lung is very interesting and the paper should benefit from more experiments or discussion that explain the gender bias. Is the expression of Nanos3 interacting partners increased in NSCLC in females? Is Nanos3 function suppressed by testosterone or androgen receptor signaling? Since there is increased bronchiolar dysplasia in Nanos3 NSCLC females, does it correlate with enhanced expression of myofibroblast activation?

- It is confusing that in vivo there is not sign of metastasis in Nanos3 NSCLC mice but the Nanos3 tumor derived cells are more metastatic. Does Nanos3 have a role in migration or invasion? The authors should include a better characterization of the cell lines in the manuscript. Do these cells exhibit enhanced expression of migration or invasion markers? Do the levels of Nanos3 correlate with higher invasive potential?

- There are some graphs that lack units or do not show standard deviation or statistical analysis, which should be included in the figures and figure legends.

- Histology sections in figure 3 is too small to appreciate differences, I recommend to include panels with bigger magnification or accompany with quantitation (same in figure 5 and 7).
Minor comments:

- Background section shouldn't exhibit references to figures, I recommend to include references from the literature.

- Define what is exactly the meaning of "ectopic" expression, and discuss whether the expression of Nanos3 in the tumors is found in cancer cells or also in tumor stroma.

- The authors should change the blot shown in figure 2A with a stronger exposure of Nanos3, and include a loading control in the same panel.

Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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