**Author's response to reviews**

**Title:** Characterization of human malignant mesothelioma cell lines orthotopically implanted in the pleural cavity of immunodeficient mice for their ability to grow and form metastasis

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**Author's response to reviews:**

Dear Editor,

In relation to the manuscript 1398630894756530 - "Characterization of human malignant mesothelioma cell lines orthotopically implanted in the pleural cavity of immunodeficient mice for their ability to grow and form metastasis", by myself et al., here is a reply to the critiques of the reviewer on a point by point basis.

1) This is the fourth revision of the manuscript. This criticism as been raised by dr. Onn in the first revision (point 3), but not in the second and in third, so we assumed that we had answered properly to these points. We answered to this point in the first review of the manuscript.

2) Again, we answered to this point in the first review of the manuscript (point 1).

3) As clearly reported in the manuscript (tables 2,3 and 4) the tumors growth was monitored measuring the number of nodules and also their dimensions. We chose this method because we find it more accurate in determining tumors development. Dr. Onn referred to the recent paper from Sone's group in which the authors, to asses the effects of a drug, only reported the tumors weight range and median weight. However, the results proposed in this paper clearly show that this method was inadequate as the weight range of different treatment groups were overlapping and performing a statistical analysis, these results wouldn't be significantly different. Also for these reasons we chose to precisely describe the tumors growth progression. In this contest, the effects of drugs can be measured comparing the number and the dimensions of tumor nodules.

4) Recent findings showed that Mesothelin and TTF-1 have a limited value in assisting in the diagnosis of Mesothelioma.

1) Ordonez NG, Application of mesothelin immunostaining in tumor diagnosis.

The complete markers analysis we performed allowed us a clearly characterize the tumor masses. CEA and BerEP4 are adenocarcinoma specific markers and therefore are nor expressed by mesothelioma. Calretinin and HBME-1 are positive markers shared by both epithelioid and biphase variants of mesothelioma, whereas CD15 is a negative marker. Surface expression of the epithelial membrane antigen (EMA) is a marker that discriminates between reactive proliferation of mesothelial cells and malignant mesothelioma. The epithelia of biphase mesotheliomas show strong reactivity for Cytokeratin 8/18, whereas Podoplanin is the most recently recognized marker for epithelioid mesotheliomas.

5) The manuscript has been revised by a native English medical writer. Red has been changed with read.

Thank you very much for your attention,

Sincerely,

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