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Letter

Response to "High CD44 expression is not a prognosis marker in patients with high-risk neuroblastoma"

Francisco M. Vega[a,*], Ana Colmenero-Repiso[b], María A. Gómez-Muñoz[b], Ismael Rodríguez-Prieto[b], Diana Aguilar-Morante[b], Gema Ramírez[c], Catalina Márquez[c], Rosa Cabello[d], Ricardo Pardal[b,*]

[a] Dpto. de Biología Celular, Universidad de Sevilla and Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Reina Mercedes 6, 41012 Seville, Spain
[b] Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla and Dpto. de Fisiología Médica y Biofísica, Universidad de Sevilla, IBiS. Avda. Manuel Siurot s/n, 41013 Seville, Spain
[c] Unidad de Oncología Pediátrica. Hospital Universitario Virgen del Rocío, Spain
[d] Unidad de Cirugía Pediátrica, Hospital Universitario Virgen del Rocío, Spain

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We are grateful for Dr. Janoueix-Lerosey and colleagues pointing out the labelling mistakes in Figure 1 on our original publication [1]. We apologize for the confusion these mistakes have caused and have published a Corrigendum to correct them, together with extra discussion and methods [2]. These changes do not affect the conclusions of the manuscript. We do not agree with the Letter authors' other considerations. We have presented our points to the editor and the survival data in question has been further revised by two independent reviewers after publication (one with clinical expertise and one with statistical expertise), making us confident of the data and approaches presented in the manuscript. For the two latter points in the Letter: (3) We have further clarified our patient classification strategy based on CD44 expression, including the use of the Kaplan-scan feature and the averaged 10% expression threshold used. The analysis has been performed with a setting of minimum 8 patients per group as can be observed in Fig. 1 and replicated with the original data. There might be a disparity of opinion about how patients should be classified, but no statistical methodology concern; (4) All survival curves show significance using the LogRank test, although small degrees of significance are achieved due to limited samples per group. Significance can also be achieved when considering high or low CD44 expression in the context of other clinical parameters, like for example in patients with age higher than 18 months at diagnosis, with or without NMYC amplification Figure 1 (Fig. 1). We have observed in many cases an association of CD44 high expression with worst outcome, and we suggest this can be related to the presence of CD44-high undifferentiated cells. As discussed and referenced in our manuscript, the association between low CD44 expression and bad outcome, pointed out by the Letter, has been known for some time, but controversy remained in the field as some aggressive tumours were known to present high CD44 expression. We specifically investigate the survival of patients with the highest CD44 expression. We have discussed throughout the paper the potential significance of this double role for CD44 expression in neuroblastoma and attribute it to the presence of different CD44 expressing cell entities in neuroblastoma tumours. For this reason, we are not to establish CD44 as a prognostic biomarker by itself, and this is not the aim of the manuscript.

* Corresponding authors.
E-mail addresses: fmvega@us.es (F.M. Vega), rpardal@us.es (R. Pardal).

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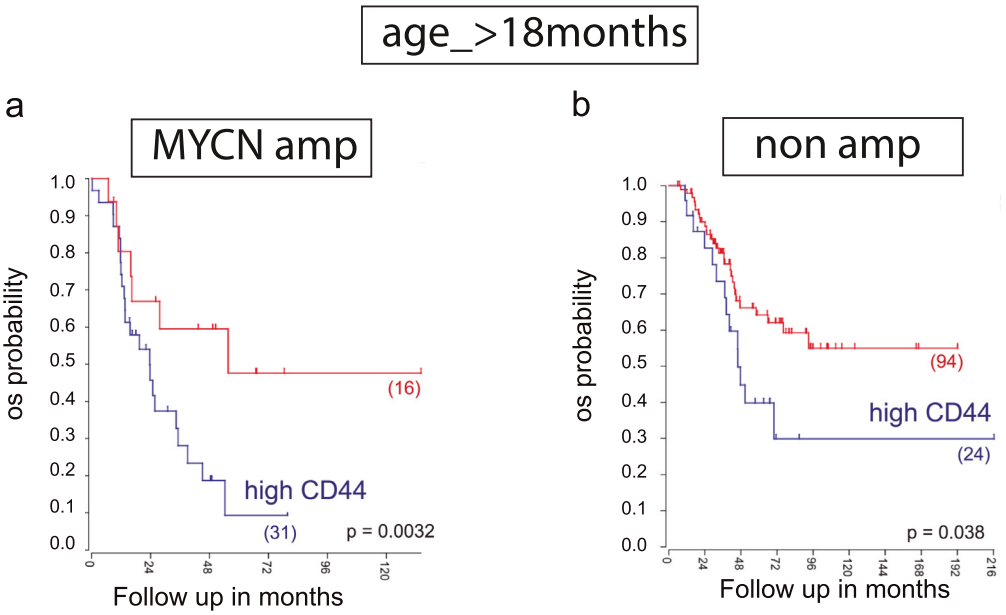

Fig. 1. **a**, Survival curves on dataset GSE45547 showing overall survival probability for tumours with high vs low CD44 when considering patients with more than 18 moths at diagnosis with MYCN amplification. tumour samples only. **b**, Survival curves showing overall survival probability for tumours with high CD44 vs rest when considering patients with more than 18 moths at diagnosis without MYCN amplification. Patient samples per group are shown in brackets. *p* values: Logrank.

Declaration of Competing Interest

The authors declare no competing interest.

References

[1] Vega FM, Colmenero-Repiso A, Gómez-Muñoz MA, Rodríguez-Prieto I, Aguilar-Morante D, Ramírez G, et al. CD44-high neural crest stem-like cells are associated with tumour aggressiveness and poor survival in neuroblastoma tumours. EBioMedicine 2019;49:82–95 https://doi.org/10.1016/j.ebiom.2019.10.041.

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