Response to Chen et al.

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Clinical and Translational Gastroenterology 2020;11: e00205. https://doi.org/10.14309/ctg.0000000000000205

We would like to thank Dr. Chen and colleagues for their comments on our recent paper on the prognostic and functional significance of OLFM4 in hepatocellular carcinoma (HCC) (1,2). The authors raised 3 interesting issues, which we would like to address in the following points.

DEFINITION OF EARLY-STAGE HCC

Our study assessed the significance of OLFM4 in a collective of patients with early-stage HCC. The condition "early stage" was defined here according to the possibility of treatment with curative intent (either by liver resection or transplantation) as determined by preoperative evaluation. Although patients with extrahepatic metastases are generally not considered eligible for surgical treatment (3,4), additional, more restrictive criteria (such as the Milan criteria) must be fulfilled for liver transplantation. As noted by the authors, 6 patients from our collective (3.8 %) turned out to have extrahepatic lesions. We thus repeated the survival analysis according to OLFM4 staining after excluding these 6 patients from our analytic cohort. We could hereby confirm that cytoplasm staining for OLFM4 is associated with poorer prognosis (Figure 1a; $P = 0.0086$ and Figure 1b; $P = 0.0075$), that survival is not affected by the presence of membrane staining (Figure 1c, $P = 0.104$; Figure 1d, $P = 0.0983$), and that the cellular localisation of OLFM4, rather than its overall staining, determines the outcome of patients (Figure 1e; $P = 0.155$). We thus conclude that the presence of these 6 patients with metastatic disease (of 151) did not bias the results of our study.

CHOICE OF CLINICOPATHOLOGICAL PARAMETERS

The authors also suggest that the presence or absence of satellite nodules and of tumour encapsulation could be assessed in addition to the clinical/pathological parameters used in our analysis. We agree that there are several additional parameters, which might contribute to determine the survival of HCC patients. Yet, a choice had to be done to avoid excessive fragmentation in the subgroup analysis of this relatively small collective. We thus chose some of the well-established parameters most used also for staging (5), although those proposed by the authors would have been interesting as well. Perhaps, the assessment of the proposed factors can represent the object of future research.

ANALYSIS OF SURVIVAL

In a third point, the authors suggest that recurrence-free survival should be assessed in the analysis of this collective. We agree with this point, which is particularly relevant in patients with an underlying liver disease, which is known to affect survival independently of tumour recurrence. However, we believe that tumour-specific survival, which was used in our analysis, can be considered a good correlate for the risk of HCC recurrence for the exploratory purposes of our study. In fact, our data (including our functional experiments) point to the fact that OLFM4 affects the tumour phenotype rather than the severity of the underlying liver disease.

We hope that these explanations will adequately address the issues raised by the authors and contribute to increase the clarity of our study. We agree that further investigation is needed to validate our findings.

CONFLICTS OF INTEREST

Guarantor of the article: Enrico N. De Toni, MD.

Specific author contributions: The 4 authors equally contributed to this letter, which is written on behalf of all the authors of the original manuscript.

Financial support: None to report.

Potential competing interests: E.D.T. has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, Pfizer, IPSEN, and Roche. He has received reimbursement of meeting attendance fees and travel expenses from Arqule, BMS, Bayer, Celsion and Roche, and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and Roche.

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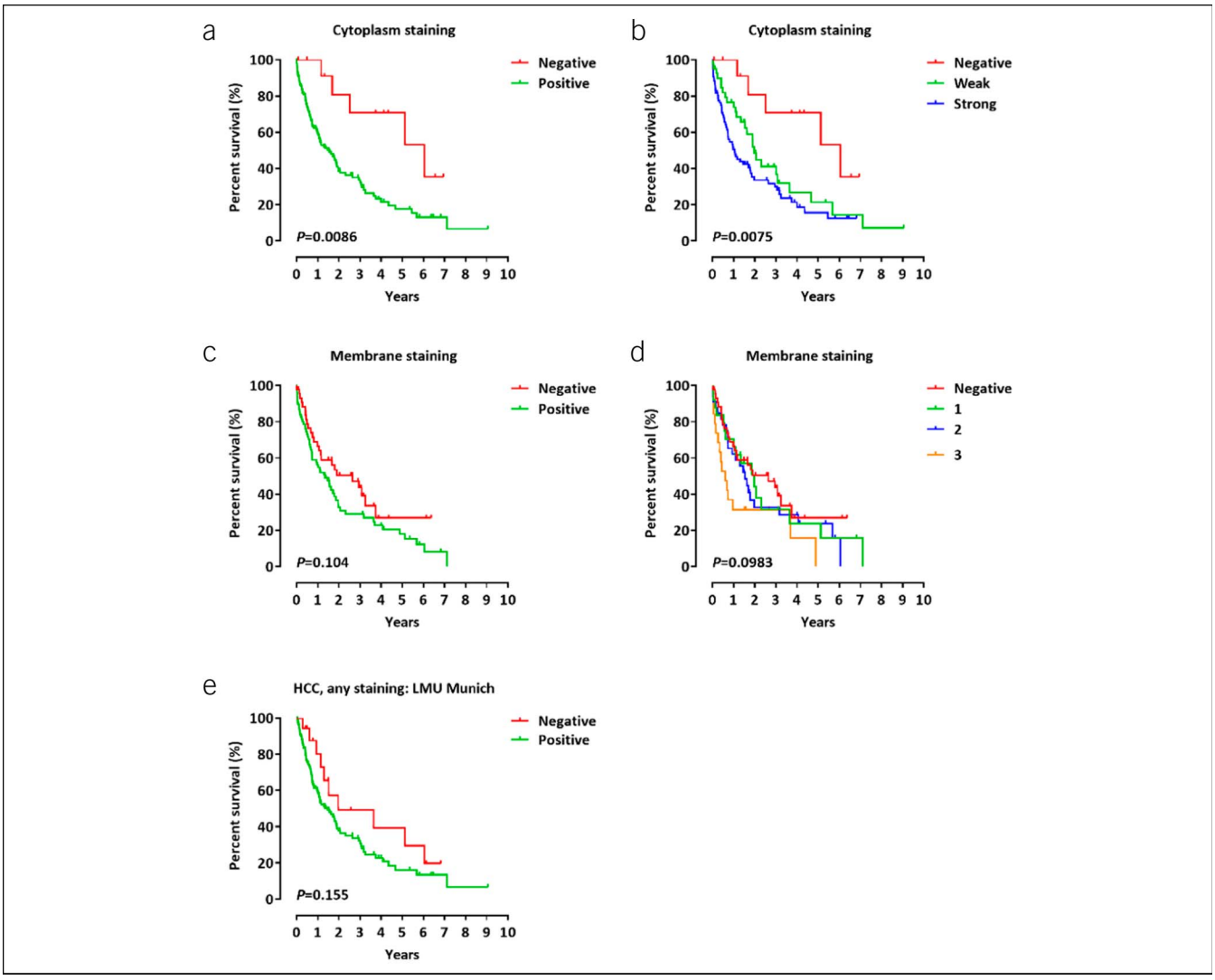

Figure 1. Effect of OLFM4 staining according to its cellular distribution in patients without extrahepatic tumors. (**a**) Tumor-related survival according to the presence or absence of cytoplasm staining for OLFM4 or (**b**) according to a semiquantitative evaluation of cytoplasm staining. (**c**) Tumor-related survival according to the presence or absence of membrane staining for OLFM4 or (**d**) according to a semiquantitative evaluation of membrane staining. (**e**) Tumor-related survival according to overall OLFM4 staining. +: Censored cases.