Authors reply to letter to the editor by Dr Degens et al.

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Authors reply to letter to the editor by Dr Degens et al.

We thank Dr Degens et al. for their interesting comments. Our study aimed at evaluating the relationship between survival of patients receiving immune checkpoint inhibitors (ICPI, targeting the PD-1 - PD-L1 pathway) and sarcopenia or cachexia in non-small cell lung cancer (NSCLC). Our study took into account other known predictive factors of ICPI efficiency, particularly tissue PD-L1 immunostaining score in all patients. We concluded that both cachexia and sarcopenia negatively influenced the outcome of patients receiving ICPI therapy.

Dr Degens et al. asked whether the term "cachexia - sarcopenia syndrome" used in our work referred to a new combine concept. We regret that this term, sometimes used in the literature as short for cachexia and sarcopenia (being even the title of a specialized journal), led to a confusion. As detailed in the method section and the results sections of our article, cachexia and sarcopenia were analysed in their current accepted definitions, i.e. as distinct variables. For instance, both variables were independent determinants of overall survival in the Cox proportional hazard model.

Therefore, we acknowledge that cachexia is defined as a metabolic syndrome mainly characterized by body weight-loss. Cachexia is considered an underlying condition of sarcopenia insofar as inflammation is its key feature. Consequently, both distinct entities frequently overlap in clinical practice. The mechanisms behind the loss of muscle mass (whether cachexia or sarcopenia) may be indistinguishable in oncologic practice and new therapeutic approaches aim at targeting both conditions.

Dr Degens et al. point out in their comment that a significant proportion of the patient population was affected by a performance status (PS) > 1 , whereas this condition was a criterion for non-inclusion in the original registration studies and in the formal approval of the ICPI in NSCLC. We agree that the off-label use of ICPI in patients with PS 2 is a limitation of our study. However, one can note that real-world observational studies of ICPI since their approvals in NSCLC included populations with a proportion of patients who would not have been accrued in the registration studies such as patients with brain metastases or patients with poor PS. For instance, the IFCT-1502 CLINIVO observational study reported real-world evidence of long-term survival with nivolumab in a French nationwide cohort of patients with advanced NSCLC [1]. In this study, despite the accrual of 170/902 (19 %), of patients affected by a PS ≥ 2 , the observed overall median survival OS was 9.7 months (95 % confidence interval: 9.0–11.1 months). We believe that patients with PS = 2 as the sole criterion against ICPI approval frequently receive a proposal of off-label immunotherapy in the routine practice as it occurred in our study. In consideration of the

interesting comment by Dr Degens et al. we tested the interaction between PS and cachexia: there was, as suspected, a significant relationship between the two variables (chi² test $p < 10^{-3}$). The three models presented in the results section were consequently ran again with the addition of the variable "interaction PS-cachexia". This variable was retained neither in the disease control rate multivariate analysis, nor in the survival multivariate analyses (PFS and OS) and consequently, the independent determinants of patients' outcome were those reported in our manuscript [2]. The conclusion that Cachexia and sarcopenia negatively influences the disease control rate and survival of NSCLC patients during anti-PD-1 ICPI therapy is supported by our study.

Among the limitations of our study, one is the current shift from immunotherapy to immunotherapy – chemotherapy combination in the first-line treatment of metastatic NSCLC. Whether the observation of the negative effect of cachexia and sarcopenia as reported by us will extend in patients receiving immuno-chemotherapy combinations remains to be established.

Declaration of Competing Interest

I hereby certify that there are no conflict of interest for any of the authors regarding the correspondence related to the article entitled:

Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors.

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