Pembrolizumab Exposure–Response Assessments Challenged by Association of Cancer Cachexia and Catabolic Clearance—Letter

Sander Bins1, Stijn L.W. Koolen1,2, and Ron H.J. Mathijssen1

Turner and colleagues (1) recently presented a hypothesis that the exposure–response relationship of pembrolizumab is confounded by cancer cachexia, because patients in the lowest quartile of exposure at doses of both 2 and 10 mg/kg have comparably bad overall survival (OS). Although at first sight this seems to eliminate the possibility of a real exposure–response relationship, they subsequently showed that clearance of pembrolizumab at baseline (CL0) influenced the HR for OS, both in melanoma and in patients with non–small cell lung cancer. To further investigate this discrepancy, they added cachexia-related factors such as albumin to a multivariate Cox regression model with CL0, which reduced (but not completely superseded) CL0 HR for OS. The latter was interpreted by the authors as strong evidence that cachexia, at least partly, explains the exposure–response relationship, but we do have our doubts about this ‘evidence’.

Primarily, CL0 was calculated using a time-dependent population pharmacokinetic (PPK) model (2), in which several baseline factors served as covariates for clearance, for example, albumin, sum of the longest diameter of the target lesions (BSLD), gender, and performance status. These covariates largely overlapped the factors added to the Cox regression model. Because of this circular reasoning, it is not surprising that CL0 HR for OS is reduced by these factors, because they have been used to improve the estimated CL0. In addition, the factors assessed are not exclusive for cachexia, but for a compromised clinical condition in general. Because the time-dependent factors assessed (i.e., change in albumin and weight) comprised the period from baseline up to week 9 of treatment, these factors may merely indicate which patients are deteriorating during treatment and thus have worse survival. Therefore, this will not differentiate between cachexia or any other explanation for this deterioration. Finally, tumor size was part of both the PPK model and the Cox analysis, but unfortunately measurements were not mentioned in the manuscript. This leaves room for speculation on the impact of tumor size: it might indeed cause worse clinical condition at baseline, but since pembrolizumab clearance also appears to be dependent of BSLD, it could be that the necessary drug concentration is not reached at higher tumor volumes. As a similar exposure–response relationship has been identified for nivolumab (3), the underlying mechanism of this unexpected finding needs to be explored further. Although plausible, the cachexia hypothesis remains highly premature and we should be careful to not exclude other theories yet.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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