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Reply to Seban et al. Letter to the Editor.

Title: Defining hyper-progressive disease using tumor growth rate: what are limitations and shortcuts?

Running title: Shortcuts in Tumor Growth Rate

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REPLY: We thank Seban and colleagues for their interest and their insightful comments on our study (1). We very much agree with the authors on the remarkable potential role of the quantitative parameters derived from 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) in predicting response to immune checkpoint inhibitors (ICI). Furthermore, as emerged from the latest publications, their combination with circulating biomarkers, such as neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, circulating tumor cells, cell-free DNA, and so forth, can provide complementary information and appears rather promising in predicting clinical outcomes.

Some aspects, however, require to our opinion more thorough clarification. At first, based on the two time points, i.e. baseline and 8 weeks after ICI start, used in our study to define hyper-progressive disease (HPD) (1), Seban and colleagues affirm as follows: “patients might have been already progressing rapidly before the initiation of ICI”. Indeed, most classifications define HPD by using tumor growth rate (TGR), which considers the tumor growth during ICI treatment with a reference period immediately prior to ICI. Nevertheless, this computation of TGR, is not free from drawbacks and might underestimate the real number of patients experiencing HPD. Primarily, because the assessment of new lesions and non-measurable disease is not taken into account in the definition of TGR, while we know quite well that progressive disease often is driven by the appearance of new lesions and /or increase of non-target lesions. Secondarily, because it can be difficult to reach a TGR-doubling in tumors with higher TGR prior to treatment. For instance, an increase from 60% prior ICI to 80% during ICI treatment will not configure an HPD based on the abovementioned criteria, despite a significant absolute increase in tumor burden. In other words, using TGR might exclude HPD in tumors with large tumor burden prior to ICI. Similarly, non-measurable lesions, e.g. lymphangitis, bone metastases, and pleural or peritoneal effusions, might not be represented in whole tumor burden based on pure morphological criteria (RECIST). With this regard, we must not forget that a high number of metastatic sites can be as valid surrogate of tumor burden as emerged in previous studies (2). Along the abovementioned TGR “clinical” limits, there is also a logistical limitation: TGR computation requires a prior CT scan, which is sometimes difficult to

retrieve, e.g. 30% of the cases in the study of Matos and colleagues (3). Therefore, in our criteria we included also time to treatment failure (TTF), which can be clinically useful when TGR cannot be evaluated.

Last, but not least, Seban et al. highlight the high prevalence of HPD in our study, i.e. 30%, compared to other series. Besides the different criteria used in defining HPD, most of other studies include all tumor types, while our cohort is limited to non-small cell lung cancer patients. When considering only this tumor type, our results are quite consistent with those from other publications dealing with similar patients' cohort (2).

At the very end, what comes out of our study is that we were able to identify a subgroup of patients with worse outcome during ICI therapy, and this is already a relevant evidence, independently if it caused by the treatment itself or by the intrinsic behavior of the tumor. In our opinion, distinction between fast and accelerated progression is still premature and it is a pure semantic license so far, because methods proposed for HPD have their own limitations. Therefore, a universally accepted consensus on how to define and to measure HDP is necessary, and this is in line with our conclusions and those derived from Seban and colleagues in their letter to the editor.

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