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REPLY: We thank Seban et al. for their interest and their insightful comments on our study (*1*). We very much agree with them on the remarkable potential role of the quantitative parameters derived from ^{18}F-FDG PET/CT in predicting response to immune checkpoint inhibitors (ICIs). Furthermore, as has emerged from the latest publications, the combination of ICIs with circulating biomarkers such as neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, circulating tumor cells, and cell-free DNA can provide complementary information and appears promising in predicting clinical outcomes.

However, we believe that some aspects require more thorough clarification. On the basis of the 2 time points (baseline and 8 wk after ICI start) used in our study to define hyperprogressive disease (HPD) (*1*), Seban et al. affirm that patients might already have been 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 in comparison with a reference period immediately before 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 nonmeasurable disease is not considered in the definition of TGR (whereas we know quite well that progressive disease often is driven by the appearance of new lesions or an increase in nontarget lesions) and secondarily because it can be difficult to reach a TGR doubling in tumors with a higher TGR before treatment. For instance, an increase from 60% before ICI to 80% during ICI treatment will not configure HPD on the basis of the above criteria, despite a significant absolute increase in tumor burden. In other words, using TGR might exclude HPD in tumors with a large tumor burden before ICI. Similarly, nonmeasurable lesions, for example, lymphangitis, bone metastases, and pleural or peritoneal effusions, might not be represented in the whole tumor burden based on pure morphologic criteria (RECIST). In this regard, we must not forget that a high number of metastatic sites can be as valid surrogate of tumor burden, as has emerged in previous studies (*2*). Along with the TGR clinical limits, there is also a logistical limitation: TGR computation requires a prior CT scan, which is sometimes difficult to retrieve; for example, a prior CT scan could not be retrieved in 30% of the cases in the study of Matos et al. (*3*). Therefore, in our criteria we also included time to treatment failure, which can be clinically useful when TGR cannot be evaluated.

Finally, Seban et al. highlight the high prevalence of HPD in our study, that is, 30%, compared with other series. Besides the different criteria used in defining HPD, most other studies include all tumor types, whereas our cohort was limited to non–small cell lung cancer patients. When only this tumor type is considered, our results are quite consistent with those of other studies dealing with a similar patient cohort (*2*).

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

DISCLOSURE

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$SUV_{max\text{-}V}$ for Assessing Treatment Response in ^{18}F-FDG PET Imaging of Patient-Derived Tumor Xenografts Involving Triple-Negative Breast Cancer

TO THE EDITOR: In the preclinical arm of a coclinical trial, Savaikar et al. recently optimized ^{18}F-FDG PET imaging biomarkers of response to a combined docetaxel and carboplatin therapy in patient-derived tumor xenografts involving triple-negative breast cancer (*1*). Twenty-one necrotic-core-phenotype tumors and

13 solid tumors were examined. Besides a preclinical PERCIST paradigm, 43 imaging metrics were evaluated, both in the whole tumor and in a single highest-intensity tumor slice. These metrics included SUV_{mean} obtained from various fixed percentages of the SUV_{max} thresholds (SUV_{Th}) and SUV_{mean} obtained from the voxels involved in a sphere centered at the SUV_{max} voxel (SUV_{peak}). Spheric volumes of 4, 14, and 33 mm^3 (radius of 1, 2, and 3 voxels, respectively) were considered, leading to SUV_{P4}, SUV_{P14}, and SUV_{P33}, respectively. In particular, Bland–Altman plots of test–retest data allowed us to estimate an SUV_{25} (i.e., using a 25% of the SUV_{max} threshold) reproducibility percentage (R; 95% level of confidence) of about 20% and 25% for solid and necrotic tumors, respectively (from Figs. 3C and 3G, respectively, in Savaikar et al.). Finally, a coined quantitative response assessment score favored SUV_{25} followed by SUV_{P14} as optimal metrics of response to therapy in patient-derived tumor xenograft models.

We would like to stress the central role of R in assessing treatment response for any investigated SUV metrics, that is, the minimal relative change between 2 SUVs assessed from 2 successive examinations that is required to be considered a significant difference (*2*). In this connection, we suggest that a further SUV metric, that is, the $SUV_{max\text{-}V}$ (defined as an average SUV computed from an arbitrary total hottest volume, regardless of the location of the hottest voxels included within the ^{18}F-FDG–positive lesion), might be particularly suitable in the current context involving 21 tumors with a necrotic-core phenotype (and with varying tumor dimensions), thus exhibiting a low ^{18}F-FDG uptake at the core and well-separated ^{18}F-FDG–positive areas (Fig. 2 in Savaikar et al.). Indeed, it has been previously shown, in lung cancer patients, that the R of $SUV_{max\text{-}N}$, which is an average SUV computed from the N hottest voxels (N denotes the number of pooled voxels) regardless of their location within an ^{18}F-FDG–positive lesion, was significantly lower for an N of 30 than is the R of SUV_{peak} obtained from SUV_{max} and its 26 neighboring voxels (*3*). In a subsequent study, $SUV_{max\text{-}40}$ was found to more likely represent the most metabolically active portions of tumors than was SUV_{peak}, which was obtained from the voxels involved in a 1-mL sphere centered at the SUV_{max} voxel, with close R performance (*4*). Finally, the $SUV_{max\text{-}N}$ procedure for treatment-response assessment has been described in a Takayasu-arteritis patient, emphasizing that the greater the N value, the lower the $SUV_{max\text{-}N}$ R and, hence, the more efficient the metrics (Table 1 in Caubet et al. (*5*)). Since the voxel volume may depend on the PET system, it is noteworthy that instead of $SUV_{max\text{-}N}$, one could alternatively use $SUV_{max\text{-}V}$. When comparing baseline scans with posttreatment scans, volume should be set in the scan showing the lowest total ^{18}F-FDG–positive volume but at the greatest possible value, since the greater the volume value, the lower the $SUV_{max\text{-}V}$ R.

To conclude, Savaikar et al. addressed the important issue of reaching a consensus on the reproducibility of imaging metrics for assessing response to therapy in oncology animal models (*1*). We suggest that the $SUV_{max\text{-}V}$ metrics may have a place in this toolbox, with volume set at the greatest possible value in the scan showing the lowest tumor uptake (which is expected to be the posttreatment one). Finally, in the current series, whether R of $SUV_{max\text{-}V}$ for V = 14 and 33 mm^3 might be lower than R of SUV_{25}, SUV_{P14}, and SUV_{P33} remains to be assessed.

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Lesion Detection and Administered Activity

TO THE EDITOR: There is a preoccupation in nuclear medicine imaging with the risks posed by the use of radionuclides and with reduction of administered activities (*1*). Nearly all nuclear medicine presentations include information on the absorbed or effective doses from the radiopharmaceutical under discussion. The tiny carcinogenic risk, an extra 1 in 1,000 risk from a typical diagnostic administered activity, is minimal (*2*) when the lifetime risk of cancer is up to 1 in 2 (*3*). The debatable risk (*4*) of induced cancer from the absorbed dose must be balanced against the risks of misdiagnosis and the consequent effect on potential lifesaving treatment, especially in patients with cancer. Of course, pediatric and benign disease investigation may require a more conservative approach.

Confirmation of the detrimental effects of reducing the administered activity on lesion detection can be seen in a recent paper in *The Journal of Nuclear Medicine* by Rauscher et al. (*5*). Their study, on the effect of reducing the administered activity on the sensitivity of ^{68}Ga PSMA-11 PET/CT imaging, shows that, as would be expected, the lower the simulated administered activity, the fewer the number of lesions detected. Three readers identified 21 lesions at a rate of 100%, 100%, and 90% with a baseline administered activity of 120–192 MBq and 85%, 81%, and 90% with two thirds of the baseline tracer activity.

The standard recommended activity of ^{68}Ga PSMA-11 of approximately 1.8–2.2 MBq/kg of body weight is still under debate (*6*). If between 10% and 19% of lesions are missed by a reduction of one third of an administered activity of 120–192 MBq (*5*), this may imply that potentially up to one fifth of lesions are being missed by the standard administered activity compared with increasing the administered activity by one third.

Recommended standard administered activities should be optimized using clinical and phantom studies defining the required lesion size as seen on the image, the lesion-to-background ratio, and the administered activity required to achieve this in a time during which the patient can be expected to be motionless. There is the