Editorial Commentary

# $^{18}$F-FDG PET/CT to predict tumor PD-L1 expression and response to PD-(L)1 blockade in patients with non-small-cell lung cancer

**Frank Johannes Borm, Adrianus Johannes De Langen**

Department of Thoracic Oncology, Netherlands Cancer Institute Antoni van Leeuwenhoek, Amsterdam, The Netherlands

*Correspondence to:* Adrianus Johannes De Langen, MD, MSc, PhD. Department of Thoracic Oncology, Netherlands Cancer Institute Antoni van Leeuwenhoek, Postbus 90203, 1006 BE, Amsterdam, The Netherlands. Email: j.d.langen@NKI.nl.

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

*Comment on:* Jreige M, Letovanec I, Chaba K, *et al*. 18F-FDG PET metabolic-to-morphological volume ratio predicts PD-L1 tumour expression and response to PD-1 blockade in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 2019;46:1859-68.

Submitted Feb 04, 2020. Accepted for publication Feb 26, 2020.

doi: 10.21037/jtd.2020.03.12

**View this article at:** http://dx.doi.org/10.21037/jtd.2020.03.12

Since the introduction of PD-(L)1 checkpoint inhibitor therapy for the treatment of non-small-cell lung cancer (NSCLC) there is a search for a biomarker that distinguishes responders from non-responders. A reliable biomarker has not been found yet. Tumor PD-L1 expression, assessed by immunohistochemistry (IHC) on a histological tumor sample, is at this point the most widely used and best validated biomarker. Absence of tumor PD-L1 expression predicts for a low overall response rate (ORR) of ~10%, while a tumor PD-L1 expression of ≥50% predicts for an ORR of 30% to 45% (1-3). To acquire enough tumor material in NSCLC for IHC testing and molecular analysis can be challenging. Frailty and comorbidities of patients and limited accessibility of lesions for biopsy on one hand and the increasing number of IHC and genetic tests being requested on the other hand are a constant challenge. Non-invasive techniques for tumor profiling are therefore attractive alternatives.

Multiple studies evaluated pretreatment Fluor-18-deoxyglucose positron emission tomography ($^{18}$FDG-PET) as predictive imaging biomarker for response to immune checkpoint inhibitor therapy in NSCLC. In general, these studies show that a higher total lesion glycolysis (TLG) correlates with a poor response to PD-(L)1 inhibitors (4-6). Takada *et al*. studied the correlation of PD-L1 IHC (cut-off ≥5%) with the standardized uptake value (SUV) assessed by $^{18}$FDG-PET (7). The study was conducted in an early stage NSCLC cohort and PD-L1 IHC assessment was done on resection specimens. They found that SUVmax was significantly higher in NSCLC patients with PD-L1 IHC ≥5%.

Jreige *et al*. recently published their paper in the *European Journal of Nuclear Medicine and Molecular Imaging* (8). This group evaluated the predictive value of metabolic to morphological volume ratio (MMVR) for tumor PD-L1 expression. MMVR was measured by dividing the metabolic tumor volume (delineated on the $^{18}$FDG-PET/CT) by the total tumor volume as delineated on the CT scan. MMVR showed an inverse correlation with tumor PD-L1 expression. This difference with the study by Takada *et al*. might be due to a substantial number of patients with necrotic tumors in the study by Jreige *et al*.; Necrotic tumors can have a high $SUV_{max}$, but a low MMVR.

Tumor necrosis is associated with higher PD-L1/PD-1 expression in NSCLC (9). Therefore, low MMVR seems to correlate with necrosis and a higher PD-L1 expression.

Interestingly Jreige *et al*. found a significant correlation between disease control and MMVR in 17 patients treated with PD-(L)1 blockade, while TLG was not predictive for response. Patients with disease control also showed higher PD-L1 tumor expression. Jreige *et al*. pointed out in the discussion that tumor necrosis upregulates PD-L1 expression on tumor cells. Tumor necrosis factor α (TNFα), which is an inflammatory cytokine that arises in a necrotic environment, might be responsible for this PD-L1 induction. A recent study (10) showed that not TNFα is

responsible for PD-L1 expression and response to PD-(L)1 inhibitors, but IL-6 is. IL-6 is also known to be excreted in a hypoxic pulmonary environment (11). These mechanisms might partly explain the association between response to anti PD-(L)1 therapy and tumor necrosis.

Next to using $^{18}$FDG uptake to predict PD-L1 expression and response to PD-(L)1 blockade, it is possible to use more specific tracers. A PET imaging study with $^{89}$Zirconium labeled atezolizumab in patients with NSCLC, bladder cancer or triple negative breast cancer showed remarkable results (12). Radiotracer uptake correlated with response to atezolizumab treatment, while in this study PD-L1 IHC did not. There was no correlation found between atezolizumab uptake and PD-L1 IHC. Since checkpoint inhibitors are large proteins, biodistribution from the intravascular space to their PD-L1 target takes several days. This makes these kind of PET-scans less feasible for routine care. In the study by Niemeijer *et al*. (13) a small molecule PD-L1 adnectin bound to 18Fluor correlated with PD-L1 IHC as well as tumor response in patients with NSCLC that were treated with nivolumab. The latter was not significant, possibly due to the small number of patients. Interestingly, both studies showed substantial PD-L1 tracer uptake heterogeneity between patients and also within patients between different tumor lesions. These results demonstrate the power of whole-body imaging; although at a lower spatial resolution than microscopy, it allows to image and quantify target expression for all tumor sites at the same time.

The study of Jreige *et al*. is promising in the sense that it is pushing clinicians into a new direction. $^{18}$FDG-PET derived MMVR shows a remarkable correlation with response to PD-(L)1 blockade. As most patients receive a $^{18}$FDG-PET scan before treatment initiation, it will be simple to use this biomarker in the clinic and to generate more data for research purposes. Ideally, this biomarker information should be combined with other patient statistics (pathology, performance, etc.) and possibly novel techniques like immune PET-imaging to study more complex and hopefully more reliable predictive biomarkers. In radiomics for example, hundreds of imaged features are collected from routinely performed scans. Bioinformatics and artificial intelligence are then used on these data sets. It has been shown that the predictive and prognostic value can be improved (14,15). At this moment, more research on MMVR and other $^{18}$FDG-PET derived features must be generated in larger patient groups in order to use this biomarker for clinical decision making (i.e., to direct patient treatment). Hopefully, one day, these imaging biomarkers lead to less biopsies and more individualized and effective treatment.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.12). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-35.
2. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.
4. Seban RD, Mezquita L, Berenbaum A, et al. Baseline metabolic tumor burden on FDG PET/CT scans predicts outcome in advanced NSCLC patients treated with immune checkpoint inhibitors. Eur J Nucl Med Mol Imaging 2020;47:1147-57.
5. Evangelista L, Cuppari L, Menis J, et al. 18F-FDG PET/CT in non-small-cell lung cancer patients: a potential

 

predictive biomarker of response to immunotherapy. Nucl Med Commun 2019;40:802-7.
6. Ito K, Teng R, Schoder H, et al. Prognostic value of total lesion glycolysis on pretreatment F-18 FDG PET/CT in patients with advanced NSCLC treated with nivolumab. J Nucl Med 2018;59:206.
7. Takada K, Toyokawa G, Okamoto T, et al. Metabolic characteristics of programmed cell death-ligand 1-expressing lung cancer on 18F-fluorodeoxyglucose positron emission tomography/computed tomography. Cancer Med 2017;6:2552-61.
8. Jreige M, Letovanec I, Chaba K, et al. 18F-FDG PET metabolic-to-morphological volume ratio predicts PD-L1 tumour expression and response to PD-1 blockade in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 2019;46:1859-68.
9. Reiniger L, Téglási V, Pipek O, et al. Tumor necrosis correlates with PD-L1 and PD-1 expression in lung adenocarcinoma. Acta Oncol 2019;58:1087-94.
10. Ozawa Y, Amano Y, Kanata K, et al. Impact of early inflammatory cytokine elevation after commencement of PD-1 inhibitors to predict efficacy in patients with non-small cell lung cancer. Med Oncol 2019;36:33.
11. Recoquillon S, Gómez-Guzmán M, Rodier M, et al. Non-muscular myosin light chain kinase triggers intermittent hypoxia-induced interleukin-6 release, endothelial dysfunction and permeability. Sci Rep 2017;7:13664.
12. Bensch F, van der Veen EL, Lub-de Hooge MN, et al. 89Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer. Nat Med 2018;24:1852-8.
13. Niemeijer AN, Leung D, Huisman MC, et al. Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer. Nat Commun 2018;9:4664.
14. Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014;5:4006.
15. Mu W, Tunali I, Gray JE, et al. Radiomics of 18F-FDG PET/CT images predicts clinical benefit of advanced NSCLC patients to checkpoint blockade immunotherapy. Eur J Nucl Med Mol Imaging 2020;47:1168-82.

**Cite this article as:** Borm FJ, De Langen AJ. $^{18}$F-FDG PET/CT to predict tumor PD-L1 expression and response to PD-(L)1 blockade in patients with non-small-cell lung cancer. J Thorac Dis 2020;12(7):3883-3885. doi: 10.21037/jtd.2020.03.12