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To the Editor:

We thank Dr Stoll and colleagues for highlighting the clinically important issues raised by the recent work on the PD1 axis in COPD(1, 2). In light of these findings we share their concern that the use of anti-PD-1-PD-L1 therapies in patients with non-small cell lung cancer (NSCLC) and COPD may have unwanted effects on the underlying airway inflammatory process. Pneumonitis has been reported as a side effect in 1-3% of a mixture of cancer patients treated with anti-PD-1 therapy(3), and this proportion increased to 6% in lung cancer patients(4). Recent attempts to use tumour PD-L1 expression as a biomarker for treatment efficacy and reduce side effects still reported a pneumonitis incidence of 5%(5). However, there is little available information on the COPD status of the cancer patients in these monoclonal antibody trials. Given our observation of already impaired macrophage PD-L1 expression and increased IFNγ release by the COPD lung in response to viral infection(2), further study of these treatments in NSCLC-COPD patients is clearly required.

Analysing the expression of PD-L1 is only one-side of the coin. A key determinant of the anti-PD-1 therapy-induced pneumonitis may be the antigen-specificity of the PD-1+ T cells in the COPD airway. It is conceivable that T cells may have upregulated PD-1 in order to supress their activation and protect the lung from over stimulation by colonising bacteria, such as non-typeable *Haemophilus influenzae* (NTHi), or prevent autoimmune responses to elastin(6). If such is the case, then reversing any suppression of these T cells may improve anti-bacterial immunity or indeed be detrimental and may accelerate disease progression by reducing check point control of autoimmunity. As COPD is an enormously heterogeneous condition in which key disease mechanisms are

poorly understood; further work to improve understanding and stratify risk and response is required. A research focus on the antigen-specificity of the PD-1+ lung T cells in COPD is thus likely to be informative and a collaborative approach to address these questions in a timely manner is required.

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