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LETTER TO THE EDITOR

Comment on: Relationship between the expression of PD-1/PD-L1 and ^{18}F-FDG uptake in bladder cancer

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Dear Sir,

The study by Chen et al. addresses an important question regarding the predictive value of ^{18}F-FDG uptake in assessing PD(L)-1 expression in bladder cancer [1]. Arguably, this innovative study is of major interest as multiple issues hamper the standardization of programmed cell death ligand-1 (PD-L1) scoring in tumour tissue. Recently, the Food and Drug Administration (FDA) issued a drug safety notification warning against the use of frontline single-agent immune checkpoint inhibitors in patients with urothelial carcinoma expressing low levels of PD-L1. In August 2018, PD-L1 status was incorporated into the labels for pembrolizumab and atezolizumab for existing frontline approvals for cisplatin-ineligible urothelial carcinoma. Therefore, this article shed light on a particularly relevant question from the clinical and scientific perspectives, but also raises technical issues regarding the method described.

First, the authors did not detail the staining protocol nor the antibody used to assess PD-L1 expression. Four PD-L1 assays have been approved by the FDA/European Medicines Agency (EMA) for use in urothelial carcinoma, including the Dako 28-8 and 22C3 and the Vantana SP142 and SP263 monoclonal antibodies [2]. Among these assays, divergent results have been reported in bladder cancer, leading to different PD-L1 expression detection rates, and thus providing different number of patients eligible for first-line treatment with immune checkpoint blockade [3]. The threshold of >1% for PD-L1 positivity was clearly defined by Chen et al. [1]. However, it remains unclear which PD-L1-stained cells were evaluated in their study (tumour cells, immune cells or both). The authors should have reported the PD-L1 score for each component of the tumour immune microenvironment. Indeed, variability in PD-L1 expression across the types of stained cells may lead to a variable relationship with ^{18}F-FDG uptake values.

Second, as immune checkpoint inhibitors are validated treatments in metastatic urothelial cancer, it would have been of interest to evaluate the correlation between ^{18}F-FDG uptake and PD-L1 expression in metastases rather than in the primary tumour. Indeed, PD-L1 expression in the primary tumour can easily be determined by endoscopic transurethral resection. Five immune checkpoint inhibitors have obtained accelerated approval by the FDA for the treatment of metastatic bladder cancer [4], and molecular and functional imaging is increasingly recognized as a reliable tool for cancer staging [5, 6]. Burgess et al. recently reported a discordance in the expression of PD-L1 immune cells between primary and metastatic urothelial carcinoma lesions [7]. Thus, the correlation between ^{18}F-FDG uptake and PD-1/PD-L1 expression in distant metastases may be more variable.

Third, non-muscle-invasive bladder cancer (NMIBC) represents more than 70% of bladder cancers at the time of diagnosis. NMIBCs are often detected as a subcentimetre thickening of the bladder wall. Approximately one third (13/38) of tumours analysed by Chen et al. were NMIBC disease [1]. In this situation, ^{18}F-FDG uptake for most of the tumours of stage pT1 or less may have been underestimated due to the partial volume effect. It is well known that this phenomenon leads to underestimation of uptake intensity in small or thin structures (i.e. approximately <8–12 mm depending on the full-width at half-maximum of the reconstructed image resolution) [8]. Tumour size (presumably in the great axis) was included in the multivariate analysis, but the thickness was not. In addition, stromal lymphocyte infiltration is associated with tumour invasion depth in bladder cancer of stage pT1,

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suggesting that immune infiltration is different between muscle-invasive and non-muscle-invasive tumours [9]. Indeed, most of the tumours of stage pT1 or less were negative for PD-1 and PD-L1, which may have biased the results.

Arguably, predicting and monitoring the response to immune checkpoint inhibitors will become key issues in the near future. Numerous phase III trials evaluating anti-PD(L)1 immune checkpoint inhibitors in the settings of both localized and advanced bladder cancer are ongoing. Metabolic and molecular imaging will have a major impact on patient management in the new era of cancer immunotherapy. The study reported by Chen et al. has taken the first step in a very promising direction [1].

Compliance with ethical standards

Conflicts of interest None.

Ethical approval This article does not describe any studies with human participants performed by any of the authors.

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