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Letter to the Editor

Reply to Thomas Gevaert, Markus Eckstein, Rodolfo Montironi, and Antonio Lopez-Beltran's Letter to the Editor re: Maud Rijnders, Astrid A.M. van der Veldt, Tahlita C.M. Zuiverloon, et al. PD-L1 Antibody Comparison in Urothelial Carcinoma. Eur Urol 2019;75:538–40

We thank Dr. Gevaert and colleagues for their interest in our manuscript [1]. We agree that there are technical, practical, and cost efficiency reasons for the use of an interchangeable PD-L1 assay. Several PD-L1 concordance studies have now been published for urothelial cancer (UC) [1–5] and non-small-cell lung cancer [6–9]. The concordance rates observed are promising, suggesting that interchanging of PD-L1 assays might be feasible. Because of the implications for clinical decision-making, when interchanging the commercially available PD-L1 assays it is important that the predictive value of each assay is comparable for different immune checkpoint inhibitors (ICIs). However, none of the previously published concordance studies included prospective data regarding treatment response to anti-PD1/PD-L1 immunotherapy.

To date, results on the predictive value of PD-L1 expression in UC patients treated with PD-1/PD-L1 blockade are conflicting. For example, the objective response rate and median overall survival (mOS) to second-line atezolizumab (anti-PD-L1) treatment were better for patients with high PD-L1 expression (immune cell expression $\geq$5%) [10,11]. By contrast, high PD-L1 expression had a negative predictive value for atezolizumab in the first-line (cisplatin-ineligible) setting [12]. Despite these conflicting results, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) restricted first-line atezolizumab (approved indication) to PD-L1-positive patients only [13,14]. This decision was based on unpublished data from the ongoing first-line IMvigor-130 trial. For pembrolizumab (anti-PD-1), PD-L1 expression (combined positive score [CPS] $\geq$10) did not appear to have predictive value in the pivotal second-line Keynote-45 registration trial [15]. However, in the first-line (cisplatin-ineligible) setting, mOS was a robust 7 mo longer for patients with positive versus negative PD-L1 status [16]. On the basis of interim efficacy data from the ongoing Keynote-361 trial, investigating first-line pembrolizumab versus chemotherapy versus pembrolizumab plus chemotherapy, the FDA and EMA have restricted the use of pembrolizumab in cisplatin-eligible patients (approved indication) to those with a CPS $\geq$10 [13,14].

Inconsistencies in the predictive and prognostic value of PD-L1 expression may result from differences between companion diagnostics, but more factors might be involved. Little is known to what extent the tumor specimen (primary tumor or lymph node or visceral metastasis), surgical type (biopsy, transurethral resection of bladder tumor or surgical resection), specimen age (fresh or archival tissue), previous (neo)adjuvant therapies, and tumor heterogeneity affect PD-L1 assessment [10,17–19]. Furthermore, the intrinsic mechanism of action of anti-PD1/PD-L1 ICIs may differ and therefore may also result in a different predictive value of PD-L1 expression.

In conclusion, we agree with the considerations by Dr. Gevaert and colleagues that we cannot interchange PD-L1 assays on the basis of the available studies. Therefore, companion diagnostics should preferentially be used with their specific PD-L1 scoring algorithm per ICI. In light of the conflicting data and limited predictive value of PD-L1 expression for ICI therapy in UC, we believe that, to date, PD-L1 expression alone is insufficient for adequate patient selection and that further research is needed to identify better (combinatory) markers.

Conflicts of interest: Maud Rijnders has nothing to disclose. Astrid A.M. van der Veldt has received consultancy fees from MSD, BMS, Pfizer, Eisai, Roche, Novartis, Ipsen and Sanofi. Ronald de Wit has received consultancy and speaker fees from Merck and Sanofi, consultancy fees from Roche, Janssen and Clovis, and research funding from Sanofi and Bayer. Geert J.L.H. van Leenders has received consultancy fees from Roche and research funding from Roche and AstraZeneca.

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