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European Association of Urology

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 read with great interest the paper by Rijnders and colleagues [1] on their PD-L1 antibody comparison in urothelial carcinoma (UC). The US Food and Drug Administration and the European Medicines Agency recently restricted use of the anti-PD1/PD-L1 drugs Keytruda (pembrolizumab) and Tecentriq (atezolizumab) as monotherapy in adult patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy to individuals with PD-L1-positive tumours. Therefore, PD-L1 immunohistochemical testing is now required in selected UC patient populations.

There are three commercially available in vitro diagnostic (IVD) PD-L1 expression assays for UC, each with a corresponding manufacturer's specific algorithm. Pathology laboratories are very interested in interchangeable PD-L1 tests for several technical, practical, and cost-efficiency reasons. Therefore, many harmonisation studies on PD-L1 antibody clones have been performed in non-small-cell lung cancer (NSCLC), for which PD-L1 testing has been clinically implemented for several years [2]. The NSCLC data are promising, but it is evident that we need separate harmonisation data on PD-L1 in UC, especially because of the existence of three different scoring algorithms (as opposed to one for NSCLC) and the combination of IC and TC scoring (as opposed to TC only for NSCLC).

At present only a limited number of harmonisation studies on PD-L1 assays for UC have been published [1,3–5]. There are divergent conclusions regarding harmonisation between these studies, and differences in study design (eg, variability in selected antibody clones) are likely to be at least partly responsible [1,3–5]. One of the major limitations in the available studies is the unique focus on combined assay/algorithm concordance. Given the complexity of PD-L1 testing in UC compared to NSCLC, harmonisation studies in UC should focus on assay concordance (comparing different assays with the same algorithm), on algorithm concordance (using a single assay to compare different algorithms), and on combined assay/algorithm concordance (comparing different assays using the specific algorithms). In an ideal world we can reach concordance between different assays and algorithms, which would allow us to apply a single scoring algorithm to different interchangeable PD-L1 assays, leading to the same treatment decision. Other limitations in the available UC harmonisation studies are the use of tissue microarrays (hampering the evaluation of tumour heterogeneity), the very low numbers of evaluating pathologists (limiting the interobserver variability), the absence of assay concordance data, and the lack of prospective validation and response data [1,3–5].

When we consider the complex nature of PD-L1 testing in UC compared to NSCLC and the few concordance studies available with their major limitations, we think that at this stage it is not feasible to draw reliable conclusions regarding assay and/or algorithm concordance in UC. With the scientific knowledge currently available, we would advise use of a specific validated PD-L1 assay with the appropriate clinically validated algorithm when a PD-L1 test is needed. Large-scale harmonisation studies taking into account the specific complexity of UC testing are needed to provide pathologists and treating clinicians with confident and reliable data on the interchangeability of different PD-L1 assays and scoring algorithms [6].

Conflicts of interest: Thomas Gevaert has received consultant honoraria from Histogenex and speaker honoraria from AstraZeneca and Astellas. Markus Eckstein sits on advisory boards for AstraZeneca and Janssen-Cilag and has received speaker honoraria from AstraZeneca, Astellas, and Roche. Rodolfo Montironi has received speaker honoraria from AstraZeneca and Roche. Antonio Lopez-Beltran has received speaker honoraria from AstraZeneca and Roche.

References

[1] Rijnders M, van der Veldt AAM, Zuiverloon TCM, et al. PD-L1 antibody comparison in urothelial carcinoma. Eur Urol 2019;75:538–40. http://dx.doi.org/10.1016/j.eururo.2018.11.002.

[2] Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. J Thorac Oncol 2018;13:1302–11. http://dx.doi.org/10.1016/j.jtho.2018.05.013.

[3] Eckstein M, Erben P, Kriegmair MC, et al. Performance of the Food and Drug Administration/EMA-approved programmed cell death

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https://doi.org/10.1016/j.eururo.2019.01.038

ligand-1 assays in urothelial carcinoma with emphasis on therapy stratification for first-line use of atezolizumab and pembrolizumab. Eur J Cancer 2018;106:234–43. http://dx.doi.org/10.1016/j.ejca.2018.11.007.

[4] Hodgson A, Slodkowska E, Jungbluth A, et al. PD-L1 immunohistochemistry assay concordance in urothelial carcinoma of the bladder and hypopharyngeal squamous cell carcinoma. Am J Surg Pathol 2018;42:1059–66. http://dx.doi.org/10.1097/PAS.0000000000001084.

[5] Zavalishina L, Tsimafeyeu I, Povilaitite P, et al. RUSSCO-RSP comparative study of immunohistochemistry diagnostic assays for PD-L1 expression in urothelial bladder cancer. Virchows Arch Int J Pathol 2018;473:719–24. http://dx.doi.org/10.1007/s00428-018-2453-7.

[6] Massari F, Di Nunno V, Cubelli M, et al. Immune checkpoint inhibitors for metastatic bladder cancer. Cancer Treat Rev 2018;64:11–20. http://dx.doi.org/10.1016/j.ctrv.2017.12.007.

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