Editorial Commentary

PD-L1 testing in urothelial carcinoma: are we there yet?

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Cisplatinum-based chemotherapy is the standard treatment modality of patients with locally advanced or metastatic urothelial cell carcinoma. Due to its toxicity, however, a significant number of patients is ineligible for this treatment. In 2018 the Food and Drug Administration (FDA) has approved Keytruda (pembrolizumab) and Tecentriq (atezolizumab) for the treatment of patients who are not eligible for cisplatinum-containing chemotherapy and whose tumors express PD-L1 (1). A positive PD-L1 test result is defined as a Combined Positive Score (CPS) ≥10 using the 22C3 antibody clone for Keytruda, and as immune cell staining covering ≥5% of the tumor area using the SP142 clone for Tecentriq. In another study, urothelial cancer patients with ≥25% of either PD-L1 positive tumor cells or immune cells using the SP263 antibody had higher response rates to durvalumab as second-line therapy than those with lower expression (2). The application of different PD-L1 antibody clones, scoring algorithms and cut-off values in clinical trials raises the question on how to implement companion diagnostic testing in pathology practice and whether assay outcomes are comparable.

Several studies have compared PD-L1 immunohistochemical assays in urothelial cell carcinoma (3-8). In general these studies report overall good comparability of antibodies for PD-L1 expression in tumor cells with more variability in immune cells (3,6). Urothelial carcinoma is a heterogeneous disease with divergent differentiation occurring in up to one-third of cases. Most studies on PD-L1 expression have been performed on pure urothelial carcinomas but it is not clear yet whether these results are representative for tumors with predominant variant histology.

In a recent study in the *American Journal of Surgical Pathology*, Reis and colleagues investigate whole-slide PD-L1 expression using 22C3, SP142 and SP263 assays in a cohort of 84 urothelial cancers with predominant variant histology (9). Of interest, the authors found a particularly high expression of 88% in urothelial cancers with squamous differentiation, which was higher than in other variant histologies (17–69%) and in pure urothelial carcinoma (20–40%) (3-9). The high PD-L1 expression in urothelial carcinoma with squamous differentiation is in line with results of the second-line atezolizumab trial (IMvigor210) where increased expression was found in basosquamous-like cancer (10). Together, these results would indicate that urothelial cancers with squamous differentiation might be sensitive for immune-checkpoint inhibitor therapy.

So, is the PD-L1 assay issue resolved now for urothelial carcinoma? Unfortunately not. First of all, PD-L1 does not seem to be that robust marker as was initially suggested. While in the Reis study and the IMvigor210 trial PD-L1 expression was most abundant in basosquamous-like urothelial cancer, objective response rates for atezolizumab were only 16% in this molecular subgroup and 34% in luminal cluster II with lower PD-L1 expression (9,10). Secondly, PD-L1 assay comparisons are often done by counting percentages of positive tumor and immune cells. This indeed results in a good technical comparability, but assay specific cut-offs are applied for determination of positive or negative PD-L1 testing. Reis *et al.* demonstrate

that companion specific cut-offs resulted in 37% positivity for the SP142 assay (atezolizumab), 39% for the 22C3 assay (pembrolizumab), but only 18% for the SP263 assay (durvalumab) (9). Thus, applying companion specific cut-offs might lead to more frequent discordant results than just comparing absolute expression frequency. On the other hand, Rijnders *et al.* found most agreement between 22C3 and SP263 applying companion specific cut-offs for four PD-L1 assays (4). Thirdly, assay comparison is mostly done on tissue microarrays which facilitate studying a large number of patient samples and is less labor-intensive and cheaper than scoring whole tissue sections. PD-L1 companion testing in clinical practice is, however, done on whole tissue sections, as was also used in the current study. Due to tumor heterogeneity it is the question to what extent tissue microarrays are representative for whole tissue sections. Wang *et al.* found moderate to substantial agreement for PD-L1 expression in tissue microarray cores and corresponding whole sections, leading to discordant results in 19% of urothelial cancers (7). Finally, it is not clear yet what tissue sample is most representative for PD-L1 testing. In clinical trials available archival tissue specimens have been used. This encompassed specimens of different sampling techniques including biopsies, transurethral resections and operation specimens, different tumor sites such as bladder, lymph node and distant metastasis, in both chemotherapy-naïve and -treated patients. Comparing matched transurethral resections, cystectomies and lymph node metastasis, de Jong *et al.* found poor agreement between bladder and lymph node specimens for the SP142 assay, and that neoadjuvant therapy might affect discordant assay outcomes (11).

Various studies have shown overall good analytical comparability of PD-L1 companion assays. Nevertheless, there still remain some unresolved issues such as how to deal with PD-L1 expression heterogeneity and cut-offs. Furthermore, and maybe most important, it is not evident yet what tissue specimen and sampling technique is most representative for PD-L1 status. As an increasing number of patients is now treated with immune-checkpoint inhibitors, studies addressing these issues as well as relating different assay outcomes to actual therapeutic response rates will likely provide the answer in the near future.

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Footnote

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Ethical Statement: The author is 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.

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