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PDL1: The Illusion of an Ideal Biomarker

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There is an emerging revolution in the use of immunotherapy to treat cancer. Immune checkpoint inhibition with antibodies that target the programmed cell death 1 (PD1) pathway and its ligand (PDL1) have demonstrated significant clinical activity by providing durable benefits with minimal toxicities in multiple solid tumors, including urothelial carcinoma [1,2]. PDL1 is highly expressed in urothelial cancer of the bladder and has been correlated with pathologic stage [3] and overall survival (OS) [4].

The rapid development of PD1/PDL1 immune checkpoint inhibitors has created an urgent need for predictive biomarkers to aid in the selection of patients most likely to respond to therapy. Many clinical trials, particularly of monotherapies, have suggested that patients with PDL1-expressing tumors or tumor-infiltrating immune cells have a greater response to PD1/PDL1 inhibition [1,5–11]. Baseline PDL1 status seems to be less relevant in combination studies. However, a fairly large proportion of patients with PDL1-negative tumors also benefit from PD1/PDL1 inhibition. If PDL1 expression correlates with higher responses to PD1/PDL1 inhibitors, we could potentially induce higher responses by priming the immune system with agents such as chemotherapies that increase the expression of PDL1 in tumors.

In this issue of *European Urology Focus*, McDaniel et al reported on “Expression of PDL1 (B7-H1) Before and After Neoadjuvant Chemotherapy in Urothelial Carcinoma” [12]. This study is a retrospective analysis by immunohistochemistry (IHC) staining for PDL1 in matched samples before and after neoadjuvant chemotherapy from 40 patients with muscle-invasive urothelial carcinoma of the bladder. McDaniel et al report that PDL1 expression was significantly higher after neoadjuvant chemotherapy compared with baseline ($p = 0.0235$). Most patients received carboplatin-based neoadjuvant chemotherapy (65%) instead of cisplatin-based chemotherapy (33%) for about 3 cycles (range: 1–6). In this small study of 40 patients, McDaniel et al reported no association with PDL1 expression at baseline and pathologic stage, with tumor downstaging to lower than pT2 at cystectomy after neoadjuvant chemotherapy, with progression-free survival (PFS), or with OS.

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1. PDL1 status is dynamic

Many antineoplastic therapeutic strategies such as chemotherapy, radiation, tyrosine kinase inhibitors, and other immunotherapies have immunomodulatory properties such as inhibiting tumor-induced immunosuppressive mechanisms and increasing direct or indirect stimulatory effects on immune effector molecules [13–16], potentially making the tumor more susceptible to immune-mediated killing with PD1/PDL1 inhibitors. A biomarker study using paired biopsies from patients receiving MPDL3280A, a PDL1 inhibitor, demonstrated that treatment with MPDL3280A increased CD8 tumor immune infiltrates and PDL1 expression on tumor-infiltrating immune cells and tumor cells in patients with radiologic responses [7]. These findings support the theory that PDL1 status is dynamic; therefore, a biopsy at one time point, such as baseline, may not accurately reflect the tumor microenvironment. However, PDL1 expression may serve as an on-treatment biomarker, with upregulation confirming that the PD1/PDL1 inhibitor hit its target. Tumor PDL1 expression reflects an immune-active microenvironment [17] with activated T cells in an immunocompetent host.

2. Variability of the PDL1 antibody and immunohistochemistry reading

McDaniel et al reported on the IHC staining for PDL1 using an anti-B7-H1 monoclonal antibody (5H1) on a tissue microarray in tumor samples of urothelial carcinomas of the bladder [12]. The authors did not assess tumor immune-infiltrating cells in these samples. PDL1 expression in immune-infiltrating cells showed a correlation with response to MPDL3280A in patients with advanced metastatic urothelial carcinoma [1]. However, PDL1 expression in the tumor did not show this correlation. Although PDL1 may appear to be an ideal biomarker for predicting response to PD1/PDL1 inhibition, there is currently tremendous variability in assays and interpretation of IHC staining. Of the four common PDL1 antibody assays listed in Table 1, some measure PDL1 in the tumor, some measure PDL1 in immune-infiltrating cells, and some measure both. The assays use different cut-offs for positivity, including 1%, 5%, and an IHC score based on a sliding range. This lack of standardized PDL1 testing is a major obstacle to comparing the strength of PDL1 as a predictive biomarker across trials. Pharmaceutical companies are developing anti-PD1/PDL1 immunotherapies with corresponding companion predictive biomarkers independent of each other. Currently, there is a lack of comparative data among assays. The clone 5H1 used by McDaniel et al has been validated and was used in the initial phase 1 trials of BMS-936558 but is not commercially available. Clone SP142 is commercially available. Unfortunately, validation data for these assays are lacking, and without standardization, the value of these markers remains unclear.

The dynamic nature of the immune system poses a challenge to the development of a predictive biomarker for PD1/PDL1 inhibitors. McDaniel et al [12] failed to show the value of PDL1 expression in muscle-invasive urothelial carcinoma of the bladder as a predictive biomarker for neoadjuvant chemotherapy, since there was no correlation with response assessed by pathologic downstaging of the tumor and PDL1 expression. The study also failed to show the value of PDL1 as a prognostic biomarker, since there was no correlation with pathologic stage, PFS, or OS and PDL1 expression in this small retrospective study. Instead, the increase in PDL1 expression after neoadjuvant chemotherapy demonstrated by

McDaniel et al underscores the significant point that PDL1 status within the tumor is dynamic. Neoadjuvant chemotherapy with carboplatin- or cisplatin-based chemotherapy increases expression of PDL1 in the tumor after treatment, suggesting it has immunomodulatory properties that may make the tumor more susceptible to immune-mediated killing with subsequent PD1/PDL1 inhibition in the adjuvant setting.

PDL1 may seem like an ideal biomarker for predicting response to PD1/PDL1 inhibition, but its dynamic nature and the lack of standardization in available assays means that it is not. Baseline PDL1 expression, regardless of assay and cut-off, can enrich for patients who would respond to monotherapy with PD1/PDL1 inhibition and could serve as a stratification factor in randomized trials; patients with low PDL1 expression could be selected for combination therapeutic strategies. Finally, PDL1 expression is a critical marker of immunity status, reflecting T-cell activation in an immune-active tumor microenvironment. McDaniel et al [12] succeeded at demonstrating that the adaptive regulation of the immune response expressed by PDL1 can occur in patients with muscle-invasive urothelial carcinoma of the bladder treated with neoadjuvant chemotherapy.

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Table 1–

Selected assays for immunohistochemistry assessment of PDL1 status

Source	Monoclonal antibody	Clone	Automated	Cells evaluated	Staining location	Positive cutoff
Genentech/ Roche [7]	Rabbit	SP142	Yes	Tumor cell and tumor-infiltrating immune cells	Membrane	^IHC 0: <1% ^IHC 1: 1% to 5% IHC 2: 5% to 10% IHC 3: 10%
	Murine	22C3	Yes	Tumor cell and tumor-infiltrating immune cells	Membrane	1%
Merck [11]	Rabbit	28-8	Yes	Tumor cell	Membrane	5%
Bristol-Myers Squibb [16]	Murine	5H1	No	Tumor cell	Membrane	5%

IHC = immunohistochemistry.

* Commercially available. IHC 0 and 1 are considered negative for PDL1.