

## CCR Translations

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## The Future of Cancer Therapy: Selecting Patients Likely to Respond to PD1/L1 Blockade

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It is conceivable that, in the near future, an assay that defines the likelihood of a patient with advanced cancer to respond to immunotherapy based on PD1/L1 blockade will be the initial decision point to select the treatment of patients with any cancer type. *Clin Cancer Res*; 20(19); 4982–4. ©2014 AACR.

Therapies blocking PD1/L1 have shown unprecedented rates of durable tumor responses in a variety of cancer types (1–5). The identification and characterization of factors in the tumor microenvironment at baseline (immediately before starting treatment) that predict which patients are likely to respond to therapy have become a top priority challenge in cancer medicine. In this issue of *Clinical Cancer Research*, Taube and colleagues (6) report on the analysis of 68 tumor samples obtained from 41 patients with advanced lung, renal, colorectal, and prostate cancers as well as metastatic melanoma treated with the anti-PD1 antibody nivolumab. On the basis of the expression of PD1, PDL1, PDL2, and lymphocytic infiltration using immunohistochemistry (IHC) techniques, they found that PDL1 expression, as a single factor, showed the strongest association with response to anti-PD1 blockade. The results of this study advance our knowledge about factors in the baseline tumor microenvironment that may predict response to PD1 blockade therapy and serves as a stepping stone for further investigation. Additional work will be needed to understand if archival tissues (obtained up to 13 years before start of therapy in the current report, with a mean of 3 years for the whole series) perform similarly as samples obtained immediately before starting on anti-PD1 therapy, and if results are the same when using methodology-validated commercial grade PDL1 IHC assays.

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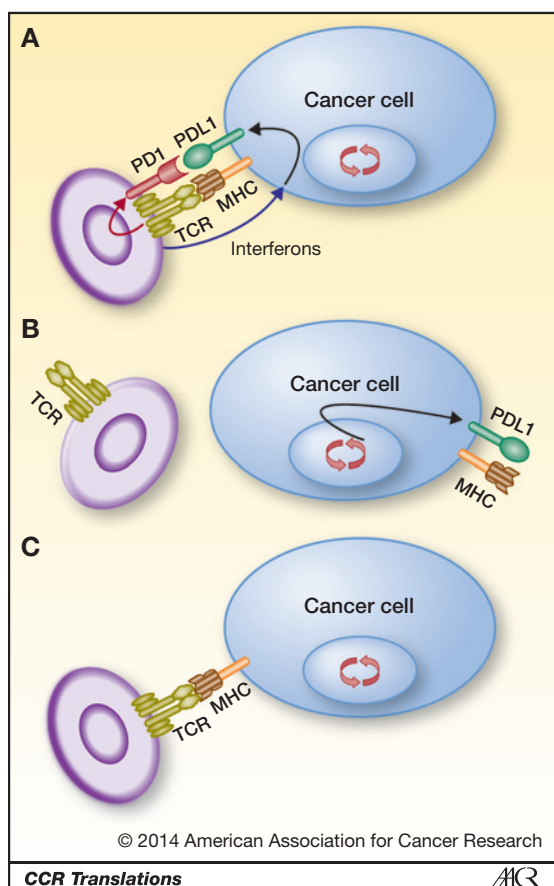
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The efficacy of PD1/L1-blocking antibodies is contingent on the presence of tumor-specific PD1<sup>+</sup> T cells being negatively regulated by PDL1-expressing cells in the tumor (7). In this situation, interrupting a functionally intact PD1–PDL1 axis with monoclonal antibodies enables T cells to mediate cancer cell killing. Key to this interaction is the detection of PDL1 expressed by the tumors as highlighted by the work by Taube and colleagues (6). However, the microenvironment where tumor cells with interferon-induced PDL1 expression interface with PD1-expressing T cells is different from that of cancer cells with constitutive PDL1 expression. Figure 1 provides several scenarios of the interaction between cells of the tumor, T cells, and PD1/L1. The expression of PDL1 can be induced by interferon-producing T cells, which was termed adaptive immune resistance by Pardoll (8). In this scenario, tumor antigen-specific T cells infiltrate metastatic lesions and specifically recognize tumor antigens through their T-cell receptor (TCR), which triggers the expression of PD1 and other activation-induced T-cell markers. These T cells also produce interferons, which in some cancer and tumor stromal cells induce the expression of PDL1 (9). If all components of the axis are intact, it is logical that therapies blocking PD1 or PDL1 have the potential to mediate tumor rejection. In some cases, PDL1 can be constitutively expressed through oncogenic processes that vary according to different cancer types (8). Evidence is scarce as to whether the constitutive oncogenic expression of PDL1, in the absence of adaptive PDL1 expression induced by T cells, is associated with antitumor activity of PD1 blockade therapy. In a third scenario, tumors may be associated with T cells that are dysfunctional; that is, they have no TCR specificity to tumor antigens, or they are not interferon-producing that lead to PDL1 and PD1 expression. The benefit of PD1/L1-blocking therapies in this scenario remains in question.

Hence, the expression of PDL1 in tumors is an important factor in determining the likelihood of a tumor regressing during PD1 blockade. However, its presence must be put within the context of additional variables that make up for a more complex equation. PDL1 expression in the absence of T cells is of unknown significance for response to PD1



**Figure 1.** Potential interactions between cancer cells and T cells limited by PD1/L1. A, adaptive immune resistance happens when a T cell with a TCR specific for a tumor antigen is activated upon antigen recognition on the surface of a cancer cell. Upon activation, the T-cell expresses PD1 and also releases interferons. The interferons are recognized by the cancer cell and lead to the adaptive surface expression of PDL1. In this case, there is a colocalization of T cells, tumor cells, PD1, and PDL1. B, in some instances, oncogenic events in the cancer cells lead to constitutive PDL1 expression, which may be independent of the presence of tumor antigen-specific T cells. C, in other scenarios, T cells may infiltrate cancers in an environment that leads to their inactivation, not triggering the production of interferons and therefore not resulting in the adaptive expression of PDL1.

blockade therapy, as is the presence of T cells in tumors without an adaptive expression of PDL1 (Fig. 1). For PD1/L1 blockade therapy to work, preexisting PD1<sup>+</sup> T cells with tumor antigen specificity that become disabled upon PDL1 engagement is likely required.

Significant efforts by several research groups as well as by industry are actively taking place to provide sensitive and specific assays to detect and quantify PDL1 expression in tumors. The current challenges surrounding the cross-reactivity, specificity, and sensitivity of PDL1 IHC antibodies

will likely be resolved with these efforts. However, a PDL1 antibody for IHC or immunofluorescence that overcomes these challenges does not have, *per se*, the capacity to fully characterize the full biology of the PD1–PDL1 interaction. The detection of the presence of T cells, in particular of cytotoxic CD8<sup>+</sup> T cells, is a standard IHC protocol, but falls short of providing information about the T-cell tumor specificity. Indirect measures of tumor specificity of T cells are the expression of TCR activation markers, of which PD1 is one, as well as CD137 (4-1BB), OX40, or TIM3. A more direct measure is the clonality of TCRs, which can be analyzed by deep sequencing approaches (10). Specific TCR engagement by the recognition of tumor antigens should lead to the release of cytokines, such as interferons, which can be detected directly by laser capture microscopy and PCR or *in situ* hybridization methods (9), or indirectly by analysis of gene expression profiling looking for signatures of inflammatory or immune response in cancers (11).

In conclusion, PD1-blocking therapies have achieved unprecedented rates of durable clinical responses in several cancers. Therefore, it is envisioned that, in the near future, instead of relying on the status of estrogen receptor or Her2/neu in breast cancer, EGFR in lung cancer, or BRAF in melanoma to decide on the first-line therapy, oncologists will want to know if a patient is predisposed to respond to anti-PD1/L1 antibody therapy as the initial decision point to select oncologic therapy. Such a predictive assay will likely need to take into account PDL1 expression as well as other variables that quantitate tumor antigen-specific T-cell infiltration leading to a dominant role of PD1/L1–negative signaling in the cancer of a particular patient.

#### Disclosure of Potential Conflicts of Interest

A. Ribas is a consultant/advisory board member for Amgen, Compugen, Daiichi-Sankyo, Flexus Biosciences, Genetech, GlaxoSmithKline, Kite Pharma, Merck, and Novartis. No potential conflicts of interest were disclosed by the other author.

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**Writing, review, and/or revision of the manuscript:** A. Ribas, P.C. Tumeh

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