

## Letter to the Editor

## PD-L1 Expression in B-cell Lymphomas and Virus-Associated Malignancies—Letter

Mads Hald Andersen

In a very important recent study, Chen and colleagues describe that PD-L1 (B7-H1, CD274) is expressed on both malignant cells and infiltrating macrophages in a subset of aggressive B-cell lymphomas (1). The article highlights the possibilities of targeting the PD-1/PD-L1 pathway in these malignancies. Interactions between PD-1 on T cells and the ligand PD-L1 (B7-H1) control the induction and maintenance of peripheral T-cell tolerance during normal immune responses. Accordingly, tumor-infiltrating lymphocytes are inhibited by PD-L1 at the tumor site because of elevated levels of PD-1 on the surface of such T cells. Indeed, blockade of either PD-1 or PD-L1 resulted in objective clinical responses (2). Remarkably, an association between objective clinical response and PD-L1 expression on tumor cells was described (2). Taube and colleagues furthermore recently described that T cells may actually trigger their own inhibition by secreting cytokines that drive tumor PD-L1 expression (3). However, the immune system itself seems also to have established a respective counteractive mechanism, that is, PD-L1-specific, CD8<sup>+</sup>, cytotoxic T cells. Thus, PD-L1-reactive T cells can readily be isolated from peripheral blood of patients with cancer (melanoma) and to a lesser extent from blood of healthy donors (4). These PD-L1-specific T cells not only recognized and killed melanoma cells as well as cutaneous T-cell lymphoma cells, but also additionally PD-L1-expressing antigen-presenting cell (APC) in a PD-L1-dependent manner (4, 5). PD-L1 can

furthermore be internalized, processed, and cross-presented on the cell surface by APC. This is notable, because soluble PD-L1 has been detected in the sera from patients with cancer. Thus, induction of PD-L1-specific T cells should boost immunity by killing of immune suppressive tumor cells as well as PD-L1-expressing stroma cells contributing to the permissive microenvironment. There is a major difference between blocking PD-L1 (or PD-1) function by antibody therapy, and generating a human leukocyte antigen-restricted T-cell response against processed and thus derived PD-L1 epitopes. PD-L1 antibodies target surface protein, whereas PD-L1-specific T cells recognize and kill cells, which are expressing PD-L1 epitopes on the surface derived from intracellular PD-L1.

It is important to note that PD-L1 additionally is expressed on normal immune cells, and is further upregulated upon activation in response to, for example, IFN $\gamma$ . Nevertheless, PD-L1-specific T cells may be immensely useful to exploit for immunotherapy against certain cancers. Although not directly related, the publication by Chen and colleagues identifies a group of cancers with vigorous PD-L1 expression that may be suitable targets for such specific immunotherapy.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Disclaimer**

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Grant Support**

This work was supported by Herlev Hospital, Novo Nordisk Foundation, Lundbeck foundation, Danish Cancer Society, and Danish Medical Research Council.

Received May 17, 2013; revised May 29, 2013; accepted May 29, 2013; published OnlineFirst June 20, 2013.

**Author's Affiliation:** Center for Cancer Immune Therapy, Department of Hematology, Copenhagen University Hospital, Herlev, Denmark

**Corresponding Author:** Mads Hald Andersen, Herlev Hospital, Herlev Ringvej 75, Herlev 2730, Denmark. Phone: 45-38682602; Fax: 45-44530176; E-mail: mads.hald.andersen@regionh.dk

doi: 10.1158/1078-0432.CCR-13-1363

©2013 American Association for Cancer Research.

**References**

- Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin Cancer Res* 2013;19:3462–73.
- Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
- Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med* 2012;4:127ra37.
- Munir S, Andersen GH, Met O, Donia M, Frosig TM, Larsen SK, et al. HLA-restricted cytotoxic T cells that are specific for the immune checkpoint ligand PD-L1 occur with high frequency in cancer patients. *Cancer Res* 2013;73:1764–76.
- Munir S, Andersen GH, Woetmann A, Odum N, Becker JC, Andersen MH. Cutaneous T cell lymphoma cells are targets for immune checkpoint ligand PD-L1-specific, cytotoxic T cells. *Leukemia* 2013 Apr 18. [Epub ahead of print].

# Clinical Cancer Research

## PD-L1 Expression in B-cell Lymphomas and Virus-Associated Malignancies—Letter

Mads Hald Andersen

*Clin Cancer Res* 2013;19:4017. Published OnlineFirst June 20, 2013.

**Updated version** Access the most recent version of this article at:  
doi:[10.1158/1078-0432.CCR-13-1363](https://doi.org/10.1158/1078-0432.CCR-13-1363)

**Cited articles** This article cites 4 articles, 3 of which you can access for free at:  
<http://clincancerres.aacrjournals.org/content/19/14/4017.full#ref-list-1>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link  
<http://clincancerres.aacrjournals.org/content/19/14/4017>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.