

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: John M. Kirkwood, MD

## Melanoma in Focus

### Immunotherapy for Melanoma Using Programmed Death 1 Checkpoint Inhibitors



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**H&O** What factors make programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) good targets for immunotherapy in melanoma?

**OH** We know that the PD-1 pathway is a good target for immunotherapy in melanoma for multiple reasons. Immunotherapy historically has been a good option for melanoma treatment, going all the way back to adjuvant therapy with interferon and high-dose interleukin 2 for metastatic disease. The immune system is highly active against melanoma, which may be related to the fact that it heads the list of cancers caused by multiple genetic mutations. This means that manipulating the immune system—such as by targeting the PD-1 pathway—has the potential to benefit these patients.

Most recently, we have seen the US Food and Drug Administration's (FDA's) approval of the first PD-1 targeted agent, pembrolizumab (Keytruda, Merck), in September for metastatic or unresectable melanoma that no longer responds to other drugs, and whose disease progresses after the use of ipilimumab and—if eligible—a BRAF inhibitor.

This agent, which is an inhibitor of PD-1, has been shown to induce tumor shrinkage, although it has not been shown to improve survival or disease-related symptoms. In addition, new strategies with adoptive T-cell therapy have strengthened the role of immunotherapy in treating melanoma.

We have been able to show that the interaction between PD-1 and PD-L1 leads to immune suppression in the mela-

noma environment. Therefore, we have been pursuing for some time the idea of inhibiting that interaction and enabling the patient's immune system to attack the tumor. Inhibiting this pathway can improve response and durable response, and we hope to be able to show a survival advantage.

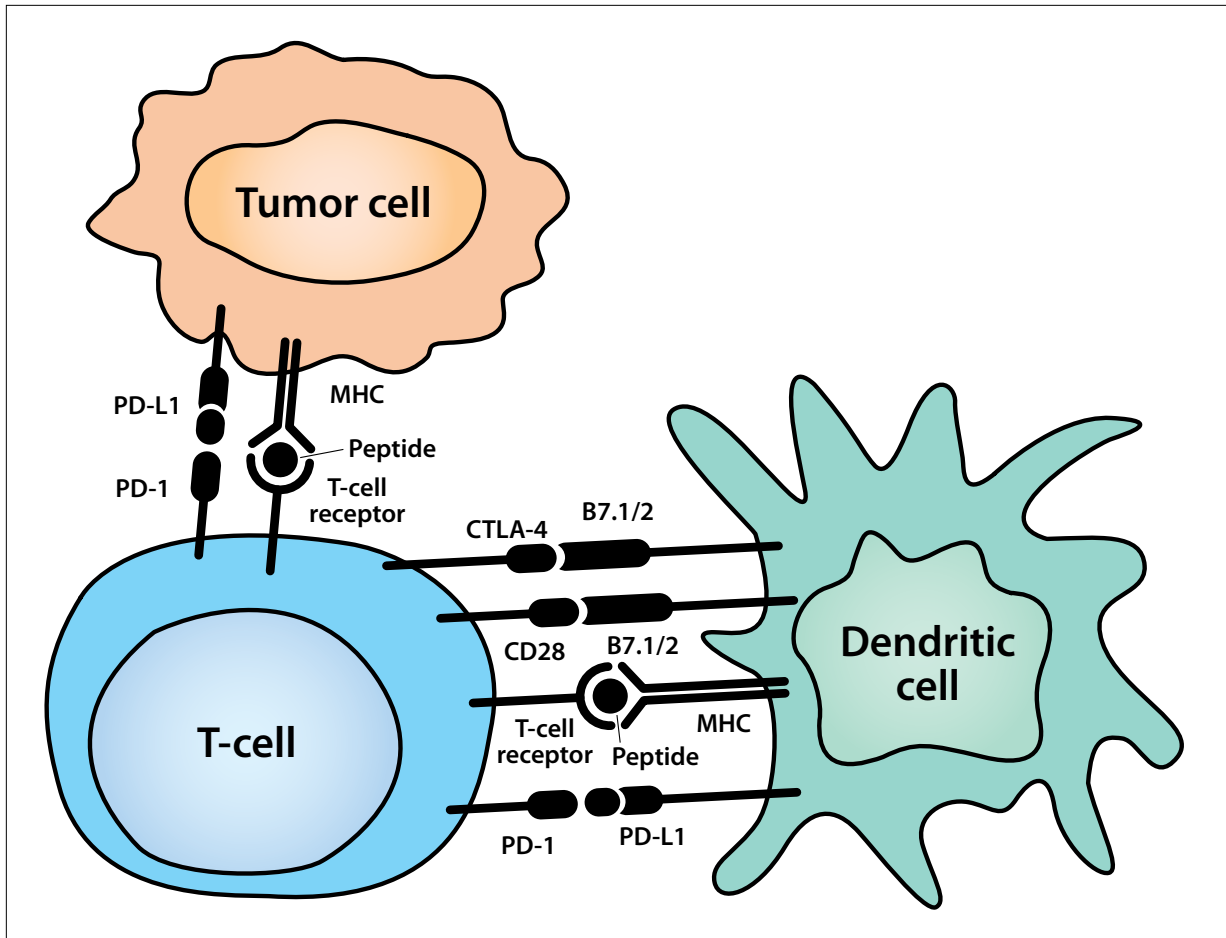
**H&O** Could you give some more detail about how PD-1 checkpoint inhibitors work?

**OH** These agents are monoclonal antibodies against the immune checkpoint receptor PD-1 and its ligand, PD-L1. We know that PD-1 and its ligands inhibit T-cell response, and that they suppress antitumor immunity as a result. Recognition of a tumor by the T-cell through the interaction of major histocompatibility complex and antigens leads to upregulation of PD-L1 and PD-L2 on the tumor. This interaction enables cancer cells to evade T-cell mediated death through immune suppression.

PD-1 expression is induced when a T-cell is activated; it is also induced by non-T-lymphocytes, B-cells, and natural killer cells. This PD-1/PD-L1 expression inhibits the immune system, inhibits our ability to target tumors, and inhibits our body's ability to recognize the tumors as foreign.

**H&O** How many anti-PD-1/PD-L1 immunotherapies are in development?

**OH** Some of the better-known ones are the PD-1 inhibitors nivolumab, which is being developed by Bristol-Myers



**Figure.** The PD-1/PD-L1 immune checkpoint.

Modified with permission from Eroglu Z, Hoffner BW, Hamid O. Checkpoint inhibition of PD-1: the promise of pembrolizumab (MK-3475) and beyond. *Immunotherapy Onc.* 2014;1(1):8-14. <http://www.personalizedmedonc.com/immunotherapy-in-oncology/april-2014-part-1>.

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

Squibb and was recently approved in Japan; MPDL3280A, which is being developed by Roche and Genentech; pidilizumab (CT-011), which is being developed by CureTech in Israel; and MSB0010718C, which is being developed by Merck Serono. There is also an anti-PD-L1 agent called MEDI4736 that is being developed by MedImmune. These agents are in different stages of clinical trials and are being studied for use in multiple tumors, including Merkel cell carcinoma and glioblastoma.

For example, nivolumab is being pursued not only in melanoma but in lung cancer, renal cell carcinoma, and a multitude of other tumors. It recently received breakthrough designation for treatment of lymphoma. MPDL-3280A is well known for its recent breakthrough designation in bladder cancer. Not only are these agents being studied singly, they are being looked at in combinatorial therapies with other immune checkpoint inhibitors and other immunotherapies, such as agents that target BRAF.

### **H&O** Could you please discuss the trial that served as the basis for approving pembrolizumab?

**OH** The efficacy of pembrolizumab was established in a clinical trial of patients with metastatic melanoma whose disease had progressed after prior treatment; some had been treated with other checkpoint inhibitors and others were checkpoint inhibitor-naïve. All of the participants were treated with pembrolizumab at either the FDA-approved dose of 2 mg/kg or a higher dose of 10 mg/kg every 3 weeks. Approximately 24% of patients had their tumors shrink, and this effect lasted for at least 1.4 to 8.5 months in most patients.

The safety of pembrolizumab was established in the whole trial population of 411 participants. The most common side effects were fatigue, cough, nausea, itchy skin, rash, decreased appetite, constipation, joint pain, and diarrhea.

What was most interesting is that this drug worked on patients who had been treated with prior

immunotherapies, including anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy and anti-BRAF therapy. Another striking finding was that these responses were durable: more than 80% of them lasted for more than 1 year. Finally, the incidence of serious toxicities was minimal and many were very manageable.

**H&O** What effect do you expect the approval of pembrolizumab to have?

**OH** We know that 76,000 people are diagnosed with melanoma and nearly 10,000 patients die of this disease each year in the United States. The fact that we have another drug that is available to patients at community health care facilities, not just to those at major melanoma centers nationally, is important. Another attribute that makes this drug a good choice for patients at community centers is the low risk of significant toxicity. I am confident that physicians in the community not only can give this therapy but can manage the side effects appropriately with their patients on an outpatient basis.

**H&O** Do you expect that this agent will eventually gain FDA approval for use as first-line therapy?

**OH** Although the drug is FDA-approved for use only in the pretreated metastatic setting, our hope is that the results from currently accrued clinical trials will support its use in the first-line setting. More importantly, we hope that planned adjuvant trials will support its future use in the adjuvant setting, where most patients with melanoma are diagnosed. Multiple trials that have already completed accrual are comparing nivolumab and pembrolizumab with standard treatments for first-line melanoma. We hope that the data will be ready to present at upcoming meetings and to submit to the FDA next year.

**H&O** What is some of the other research you are planning on PD-1 checkpoint inhibitors in melanoma?

**OH** The next step is looking at combination therapies. We currently are accruing patients to multiple PD-1/PD-L1 combinatorial studies for many solid tumors,

including melanoma, renal cell carcinoma, lung cancer, bladder cancer, and head and neck cancer. We want to learn how we can improve on the 24% rate of tumor shrinkage in melanoma, the duration of response, and the survival benefits.

**H&O** What other types of cancer might benefit from treatment with pembrolizumab?

**OH** In addition to the cancers I mentioned earlier, we are conducting small, phase 1 trials with pembrolizumab in lymphoma, glioblastoma, small cell lung cancer, and human papillomavirus-positive cancer. So, this agent is being examined in nearly every type of cancer.

**H&O** Do you think that immunotherapy will take the place of chemotherapy?

**OH** I can envision PD-1 pathway inhibitors being used in conjunction with other immunotherapies and radiation therapy, and even with chemotherapy. Chemotherapy has a role in many solid tumor therapies. We hope to show that immunotherapy is a treatment option also. Its durability of response and degree of benefit may be better than that with chemotherapy.

**H&O** Is there anything you would like to add?

**OH** I think these data are extremely promising. It is difficult to believe how far we have come, and how quickly—we now have another treatment option for our patients. The fact that pembrolizumab received approval three-and-a-half years after it first began accruing patients is a testament to the value of fast-tracking new medication.

### Suggested Readings

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res.* 2012;18(24):6580-6587.

Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med.* 2013;369(2):134-144.

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