

# Pembrolizumab is the first immune checkpoint inhibitor to receive approval for head and neck cancer

The first immune checkpoint inhibitor was approved for the treatment of head and neck cancer. was approved in August 2016. Pembrolizumab, which targets the programmed cell death 1 (PD-1) protein, is designed to reinstate the anti-tumor immune response to kill cancer cells and was approved for the treatment of recurrent or metastatic disease that progressed during or after platinum-containing chemotherapy.

The approval was based on the demonstration of durable responses, some exceeding 2 years, and good safety profile in the international, multicenter, non-randomized, open-label phase 1b KEYNOTE-012 study. A total of 192 patients with refractory/metastatic head and neck squamous cell carcinoma were enrolled in the study. The participants had measurable disease based on their scores on the Response Evaluation Criteria in Solid Tumors (RECIST [version 1.1]) and an Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status grade of 0 (fully active, able to carry on all pre-disease performance without restriction) or 1 (restricted in physically strenuous activity, but able to carry out work of a light or sedentary nature).

An initial cohort of 60 patients whose tumors overexpressed programmed cell death ligand 1 (PD-L1) were treated with pembrolizumab 10 mg/kg every 2 weeks, and an expansion cohort of 132 patients was enrolled regardless of PD-L1 status and treated with 200 mg every 3 weeks. Both cohorts were treated for 24 months or until disease progression, unacceptable safety, or investigator/patient decision to discontinue treatment.

Response was assessed every 8 weeks and the primary endpoint was overall response rate (ORR) as determined by an independent review committee based on RECIST version 1.1 scores. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and duration of response. The median age of patients was 60, 83% were men, the median number of prior therapies received was 2, and 70% of patients had an ECOG performance status of 1.

The final trial data have not yet been published, but according to a presentation at the 2016 annual meeting of the American Society of Clinical Oncology, the confirmed

## What's new, what's important

Pembrolizumab is a humanized monoclonal immunoglobulin G4 antibody that targets PD-1 and prevents it from binding to its ligands and thereby restoring T cell-mediated anti-tumor immunity. It was approved this year for the treatment of patients with recurrent or metastatic head and neck cancer that had progressed during or after platinum-containing chemotherapy.

The approval was based on findings from the phase 1b KEYNOTE-012 trial with 192 patients. Final data have not been published, but investigators have reported that the confirmed overall response rate was 17.7%, with 7 complete responses and 27 partial responses. Among the responding patients, 82% had responses of 6 months or longer, with some lasting longer than 2 years. Stable disease was achieved in 17% of patients. Responses were observed in patients with tumors that were both HPV-positive and -negative (ORR, 21.9% and 15.9%, respectively).

The recommended dose for this indication is 200 mg (administered intravenously over 30 minutes every 3 weeks). The most common adverse effects were decreased appetite and dyspnea, and 12% of patients reported grade 3 or 4 adverse effects, including pneumonia, dyspnea, vomiting, pleural effusion, and respiratory failure.

Patients should be monitored for thyroid function and clinical signs and symptoms of thyroid disorders during treatment and replacement hormones administered as deemed appropriate. Women of reproductive age should be advised to use highly effective methods of contraception during treatment and for 4 months after treatment cessation.

— Jame Abraham, MD, FACP; abrahaj5@ccf.org

ORR was 17.7%, with 7 complete responses and 27 partial responses. At data cut-off, the median duration of response had not yet been reached and responses were ongoing in more than three-quarters of the patients. Among the responding patients, 82% had responses of 6 months or longer, and some responses had lasted more than 2 years. Stable disease was achieved in 17% of patients.

Responses were observed in patients with tumors that were both positive and negative for the human papilloma virus (ORR, 21.9% and 15.9%, for patients with HPV-

## Mechanism of action: pembrolizumab

### Re-engaging T cell-mediated anti-tumor immune response

Cytotoxic T cells are key mediators of an effective adaptive immune response, including the anti-tumor immune response mounted against malignant cells that express foreign abnormal proteins on their surface that serve as antigens.

Antigen presenting cells process these antigens and present them on their cell surface in a complex with major histocompatibility complex. When they encounter a T cell, this complex interacts with the T-cell receptor on the surface of the T cell to initiate an immune response.

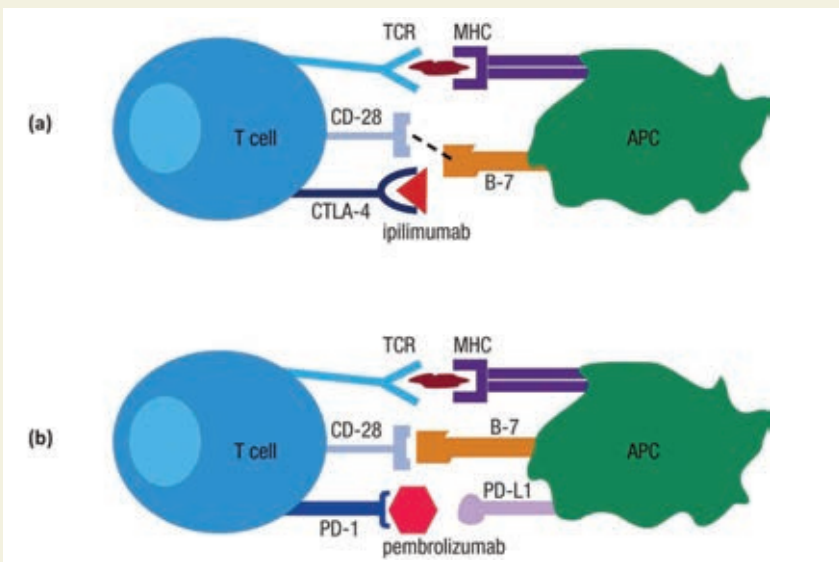
As a kind of fail-safe mechanism, a second step is required for full activation of a T cell, which involves a costimulatory signal generated by the interaction between the B7 protein expressed on the APC and a protein called CD28, expressed on the T-cell surface.

That second step can also be an inhibitory one that switches the T cell off to help limit the immune response and prevent inadvertent damage to normal, healthy host tissue. Among these inhibitory “check-point” proteins are cytotoxic T-cell lymphocyte antigen 4 and, the target of pembrolizumab, programmed cell death 1 (PD-1), both of which are engaged by the expression of their ligands on the surface of the target cell.

Tumors upregulate the expression of the PD-1 ligand on their surface and the sur-

face of the cells of the tumor microenvironment, to create an immunosuppressive environment and limit the activity of T cells that infiltrate the space around the tumor.

Pembrolizumab is a humanized monoclonal immunoglobulin G4 antibody targeting PD-1 that prevents it from binding to its ligands and therefore restores T cell-mediated anti-tumor immunity.



Pembrolizumab is a humanized monoclonal antibody targeting the inhibitory check-point protein PD-1. Blocking PD-1 from binding to its ligands that are overexpressed on the surface of the tumor prevents the T cells that infiltrate the tumor microenvironment from being switched off and helps to reinstate the T cell-mediated anti-tumor immune response. Reproduced with permission: Ho S, Kang IS, Ravnani MC. Managing advanced melanoma: targeting the PD-1 pathway with pembrolizumab. *Cancer Res Front*. 2015;1(2):127-137.

positive and -negative tumors, respectively).

The evaluation of survival was also promising, with a median OS of 8.5 months, and a 6-month PFS rate of 24.9%. As a condition of its full approval, the ongoing phase 3 KEYNOTE-040 trial is comparing pembrolizumab with 3 standard-care therapies – methotrexate, docetaxel, or cetuximab – in 466 patients with recurrent/metastatic HNSCC in the second-line setting, and is further evaluating the effects of pembrolizumab on patient survival. A second phase 3 trial is exploring pembrolizumab in the front-line setting.

The safety of pembrolizumab was evaluated in all patients receiving at least 1 dose of the drug. Treatment-related adverse events (AEs) occurred in 64% of patients, most commonly fatigue, decreased appetite and dyspnea, and 12% of patients experienced grade 3 or 4 AEs, including pneumonia, dyspnea, vomiting, pleural effusion, and respi-

ratory failure. Of the more serious AEs, only increased levels of aspartate aminotransferase and alanine aminotransferase were observed in >2 patients. No deaths occurred as a result of treatment-related AEs.

According to the prescribing information, the recommended dose and schedule of pembrolizumab for this indication is 200 mg, administered as an intravenous infusion over 30 minutes every 3 weeks. Several warnings and precautions are detailed, and specifically for HNSCC, these include hypothyroidism and embryofetal toxicity. Patients should be monitored for thyroid function and clinical signs and symptoms of thyroid disorders throughout treatment and replacement hormones administered as appropriate. Women of reproductive age should be advised to use highly effective methods of contraception during and for 4 months after treatment with pembrolizumab. Pembrolizumab is marketed as Keytruda by Merck & Co.

## References

1. Keytruda (pembrolizumab) injection, for intravenous use [prescribing information]. Whitehouse Station, NJ: Merck & Co; 2016. [https://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf). Accessed October 16, 2016.
2. Mehra R, Seiwert TY, Mahipal A, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012 [ASCO abstract 6012]. *J Clin Oncol*. 2016;34(suppl).
3. United States Food and Drug Administration. Pembrolizumab (Keytruda). <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm515627.htm>. Last updated August 9, 2016. Accessed October 16, 2016.