Merkel cell carcinoma (MCC) is an aggressive skin cancer that is caused by the Merkel cell polyomavirus (MCPyV) in virus-positive MCC (VP-MCC) or by exposure to UV light in virus-negative MCC (VN-MCC). Studies have shown that the incidence of MCC is around ten times higher in immunosuppressed populations, giving support to the idea that MCC is highly immunogenic. In VP-MCC, MCPyV integrates viral DNA into host cells which then express viral antigens that drive oncogenesis. VN-MCC has a much higher mutation rate than VP-MCC, likely due to damage from UV light. As such, the tumor cells express high levels of neoantigens. Expression of these different types of non-self antigens might allow each form of MCC to be targeted by the immune system. In the past, the only treatment for advanced MCC (aMCC) was chemotherapy. In recent years, several immune checkpoint inhibitors which take advantage of the immunogenicity of MCC have been tested. Among these are antibody therapies that bind to PD-1 or its ligand PD-L1, blocking their binding. PD-L1 on tumor cells and immune cells binds to PD-1 on T cells,
inhibiting activation and inducing apoptosis in the T cells. As T cells are a vital part of controlling cancer cells, using antibodies to block PD-1 or PD-L1 has proven to be beneficial in treating several types of cancers.

A team led by Dr. Paul Nghiem (Clinical Research Division) published a follow-up study to a multicenter phase II clinical trial on the PD-1 blocking antibody therapy pembrolizumab in aMCC in the *Journal of Clinical Oncology*. This trial enrolled patients with no previous systemic therapy for aMCC. The physicians treated patients with pembrolizumab every three weeks for up to two years. They used computed tomography (CT) to measure target lesions at different time points, as described in Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, a set of rules that defines how to evaluate solid tumors’ response to therapy. The authors found that 31 of the 45 evaluable patients in the study had target lesion reduction of at least 30%, with response time ranging from 1.5 to 9.7 months, and 28 of the patients had complete or partial response to the treatment. The median progression free survival (PFS) of patients receiving pembrolizumab was 16.8 months, a large increase over conventional chemotherapy (three months). Interestingly, there was no significant difference in responses between patients with VP-MCC and those with VN-MCC.

One of the patients in the trial only received two doses of treatment due to the development of treatment-related hepatitis. The patient was taken off of pembrolizumab and given corticosteroid therapy to reduce the hepatitis. Incredibly, those two doses were enough to initiate a complete response. The tumors shrank and were completely resolved in three years without any other cancer treatment. Nghiem noted the significance of this trial in that it has already changed the way in which patients with MCC are treated. Nghiem said, "These data were used by the FDA to grant accelerated approval for pembrolizumab in Merkel cell carcinoma in December 2018. Because this study (CITN-09/Keynote 17) was the first trial to look at using PD1 pathway blockade in MCC in patients who had not received chemotherapy before, this study has been important in changing management. The chance of a patient
responding to anti-PD1 is nearly twice as high (~60%) if they have not previously been treated with chemotherapy, and this study has thus led to changes in the NCCN Guidelines for managing this cancer.

The authors also looked at whether PD-L1 expression on tumor cells or tumor infiltrating immune cells could predict response to pembrolizumab. While overall PD-L1 expression on infiltrating cells in the tumor did not correlate with response to treatment, there was a trend towards PD-L1 expression on tumor cells and response. The authors will focus future research on the expression of multiple markers to discover which can potentially predict a response to pembrolizumab. Concerning an exciting future trial, Nghiem said, "Although half of patients with advanced MCC experience persistent benefit from anti-PD1 therapy, the other half either never benefit, or only transiently have their tumors shrink. We do not yet have reliable ways to predict who will respond to these therapies, or a clear way to help patients whose disease does not respond. Drs. Kelly Paulson and Aude Chapuis will lead a Hutch-based clinical trial using 'reprogrammed', youthful, transgenic T cells targeting the Merkel polyomavirus. That trial will enroll patients who have PD-1-refractory MCC and should open in the Spring of 2019."

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