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# Clinical activity, immune and viral correlates of PD-1 blockade with pembrolizumab as first systemic therapy in patients with advanced Merkel cell carcinoma

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*Abstract:*
Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer linked to UV exposure and the Merkel cell polyomavirus (MCPyV). Cytotoxic chemotherapy is associated with high response rates in patients (pts) with metastatic MCC, although responses are seldom durable and median progression-free survival is only 13 weeks. MCC may be responsive to PD-1 pathway blockade as tumors often express PD-L1 and MCPyV-specific T cells express the inhibitory co-receptor PD-1.
Methods: In this open-label, phase II trial by the Cancer Immunotherapy Trials Network (NCT02267603), adults with advanced/metastatic MCC and no prior systemic therapy were enrolled. Pembrolizumab, a humanized IgG4 anti-PD-1 monoclonal antibody, was given IV every 3 weeks (2 mg/kg). Response was assessed by RECIST 1.1 every 9-12 weeks. Presence of MCPyV was assessed by measuring serum antibody titers to the MCPyV oncoprotein and/or quantifying tumor oncoprotein expression by immunohistochemistry (IHC).
Results: Twenty-six pts were treated (median duration 22 weeks, range 4 to 49 weeks as of 1/8/16 dataset). Twenty-three pts had at least one documented radiologic or clinical assessment of response. Fifteen of 23 evaluable pts (65%) responded (4 complete responses and 11 partial responses); 2 additional pts had stable disease and 6 had progressive disease as best response. Fourteen of 15 responses (93%) were ongoing at last follow-up. Ten responders had at least one follow-up evaluation with response duration ranging from 8+ to 27+ weeks beyond initial documented response. Treatment was generally well tolerated with mostly grade 1 or 2 adverse events. Two pts developed severe drug-related toxicities including grade 4 myocarditis (n=1) and

grade 4 transaminase elevation (n=1), both of which improved with corticosteroid treatment. Both pts have ongoing tumor responses despite discontinuation of pembrolizumab. Sixteen of 26 pts (62%) were classified as having virus-positive MCC. Among the 23 evaluable pts, 9 of 14 (64%) of those with virus positive tumors responded, while 6 of 9 (67%) of pts with virus negative tumors responded. Analyses of T cells specific to MCPyV and titers of oncoprotein antibodies during therapy, as well as IHC characterization of tumor biopsies including PD-L1 expression are ongoing.
Conclusions: First-line therapy with pembrolizumab in pts with advanced MCC is associated with frequent (65%) and durable responses. Notably, the response rate was similar among pts with virus-positive and virus-negative tumors. While virus-positive tumors are known to express highly antigenic MCPyV oncoproteins, virus-negative tumors are typically UV-induced and display strikingly elevated mutational burdens generating putative neo-antigens. Thus, potentially through distinct mechanisms, both virus-positive and virus-negative MCC tumors appear to be immunogenic and frequently responsive to anti-PD-1 therapy.

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