559 MOLECULAR CHARACTERIZATION OF MERKEL CELL CARCINOMA AND ASSOCIATION WITH MERKEL CELL POLYOMAVIRUS

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Background Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine cancer with rapid progression and mortality rates of 33–46%.[1] The majority of MCC is caused by Merkel Cell Polyomavirus (MCPyV) with the remainder induced by UV-mediated damage.[1 2] Regardless of virus positivity or tumor mutational burden (TMB), immune checkpoint inhibitors (ICIs) are first line treatment for MCC[1] with half of patients not responding or developing resistance. Few options exist for those refractory to immunotherapy.[3] There is a need to identify the MCC-specific factors driving resistance and to identify alternate molecular targets.

Methods 205 MCC tumors were analyzed using next-generation sequencing (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). TMB was measured by totaling somatic mutations per tumor (TMB-H: ≥10 mutations/MB). MCPy viral (MCPyV) status was determined for 68 WES profiled cases using a cut-off of 1000 reads after concordance testing with IHC. Immune cell infiltrates were estimated by Quantiseq. Significance was determined using Chi-square and Mann-Whitney U tests and adjusted for multiple comparisons (q-value <0.05).

Results The majority (89.3%) of MCPyV-negative MCC tumors were TMB-high (≥10 mutations/Mb), with 96.4% having mutations in TP53 and 80.8% in *RB1*. Other gene mutations included *NOTCH1* (37%), *KMT2C* (28.6%), *TERT* (17.9%), *FAT1* (14.3%), and *PIK3CA* (14.3%). In contrast, MCPyV-positive tumors were frequently TMB-low (100%) and rarely harbored mutations in *TP53* and *RB1* (10.3% and 2.6%, respectively). Immune checkpoint gene (*CD80, CD86, CD274, PD1, PD1L,* and *CTLA4*) expression was similar between MCPyV-positive and -negative tumors. Estimated NK cell infiltration was significantly higher in MCPyV-negative tumors. MCPyV-negative MCC also had significantly higher expression of a MAPK pathway activation signature (MPAS).

Conclusions MCPyV-positive and -negative MCC represent two classes of molecularly distinct tumors and can be differentiated based on their TMB and mutational profile. The significantly increased NK cell infiltration seen in MCPyV-negative MCC represents a potential therapeutic pathway with the efficacy of NK cell-stimulating agents currently under investigation in the Quilt-3.063 trial.[4] MPAS up-regulation in MCPyV-negative MCC suggests that MAPK inhibitors could be used as an alternative to ICIs, which is supported by preclinical data.[3 5] MCPyV-negative and -positive MCC are distinct tumor subtypes whose molecular and immune cell profiles warrant further investigation to optimize use of current ICIs and identify therapeutic targets.

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Ethics Approval This study was conducted in accordance with guidelines of the Declaration of Helsinki, Belmont report, and U.S. Common rule utilizing retrospective, deidentified clinical data in keeping with 45 CFR 46.101(b)(4). Therefore, this study is considered Institutional Review Board (IRB) exempt and no consent was necessary from the subjects.

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