Background Merkel cell carcinoma is a rare cancer for which the standard-of-care is immune checkpoint blockade in the recurrent/metastatic setting. However, immunotherapy is not effective in all patients. A greater understanding of molecular mechanisms and potential predictive biomarkers are unmet needs for clinicians and researchers.

Methods We undertook a retrospective analysis of 45 patients treated at our institution from 2013 to 2020 to understand the clinical and genomic correlates of clinical benefit from immunotherapy. We gathered data from the electronic health record, including provider notes and results from our institutional next-generation sequencing panel of actionable genomic alterations.

Results Our cohort predominantly included individuals with stage III disease at diagnosis and stage IV disease at the time of diagnosis of recurrent/metastatic disease. Most patients received immunotherapy in the first line. 43% of patients experienced an objective response to immunotherapy (median duration of response 24.2 months, 95% confidence interval 9.0–28.7 months) (median follow-up 25.2 months). Lower stage at diagnosis of primary disease and shorter disease-free interval between completion of initial treatment and recurrence were each associated with greater odds of response (odds ratio of 0.06, p=0.04 for stage; odds ratio 0.75, p=0.05 for disease-free interval). The most common single-nucleotide variants among the sequenced cohort were those in TP53 (59%) and RB1 (51%). Single-nucleotide variants in the ARID2 and NTRK1 genes were associated with response without Bonferroni correction (p=0.05), while none of Merkel cell polyomavirus status, total mutational burden, ultraviolet mutational signatures, and copy-number alterations predicted outcomes (figure 1).

Conclusions Patients with shorter disease-free interval after definitive treatment may be particularly suitable candidates for immunotherapy. Our molecular findings point to ARID2 and NTRK1 as potential predictive markers and/or therapeutic targets (e.g., with Trk inhibitors), although this association needs to be confirmed in a larger sample.

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Ethics Approval The study was approved by the Dana-Farber institutional review board, protocol numbers 11–104 and 17–000.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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Abstract 306 Figure 1 Mutation landscape by immune checkpoint inhibitor response. Mutational plot showing the most frequently mutated genes (top-to-bottom, >15% ordered by response and by total number of SNVs, with gene frequency listed at left (%), and Fisher exact test p values (response versus no response) at right. Asterisks denote values less than 0.05 (significant before Bonferroni correction, for which cutoff for significance is 0.0001 for our panel of 447 genes). The bar graph at top shows the total number of panel single nucleotide variants detected per sample by mutation signature. Blank MCPyV and TMB denote unknown values.
of interferon (IFN)-gamma or CD8+ tumor cells. In addition, these subgroups were further broken down based on the proportion of programmed death-ligand 1 (PD-L1)-expressing tumor-infiltrating cells as PD-L1+ (≥1%) or PD-L1– (<1%).

**Results** Patients treated with P+V+C with high and low TMB had similar PFS outcomes. However, the magnitude of the PFS benefit with A+V+C vs P+V+C was markedly higher in patients with high TMB (≥10 mutations/Mb) compared with patients with low TMB (<10 mutations/Mb) in whom the benefit between treatment arms was comparable (figure 1A). The magnitude of the PFS benefit with A+V+C was further enhanced in patients with high TMB and PD-L1– compared with patients with high TMB and PD-L1+. Overall, patients with potential for increased antitumor immunity (IFN-gamma ≥ median or CD8+ ≥ median) who received A+V+C had more favorable outcomes compared with their counterparts with IFN-gamma < median or CD8+ < median. In general, the PFS benefit with A+V+C vs P+V+C was more readily apparent in PD-L1– subgroups. Similar trends were seen with DOR (figure 1B).

**Conclusions** There was a trend of larger magnitude of PFS benefit with A+V+C vs P+V+C in PD-L1– patient subgroups, who benefit less with single-agent immunotherapy. The PFS and DOR benefits were more evident in patients with high IFN-gamma or TMB >10 mutations/Mb. Additional multivariate analyses are ongoing to delineate the PFS trends observed.

**Trial Registration** ClinicalTrials.gov, identifier NCT02908672

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**Abstract 307 Figure 1** Forest plot of PFS (A) and DOR (B). mo, months; NE, not evaluable; Neg, negative; NE, not estimable; Pos, positive.