**Background:** MCRC with microsatellite instability (MSI-H) are associated with cytotoxic lymphocytic infiltration that is counterbalanced by multiple checkpoints. Several prospective clinical trials in chemotherapy-resistant MSI-H MCRC have demonstrated a high rate of disease control and a favorable progression free survival (PFS) with PD-1 inhibitors. However, there is a significant discrepancy in response rates (RR) with pembrolizumab and nivolumab (28% to 52%), likely reflecting patient heterogeneity. We sought to determine the RR to PD-1/PD-L1 targeting in a single center setting.

**Methods:** All MCRC patients (pts) with MSI-H tumors (by CLIA certified PCR, IHC, or NGS assays) who were treated at City of Hope with PD-1 or PD-L1 inhibitors starting Jan 2016 were identified. RR and PFS were determined by RECIST 1.1. BRAF status, primary tumor location, and metastatic sites were collected on all pts. TMB as determined by FoundationOne® on 0.83-1.1 megabases (Mb) of sequenced DNA was collected, when available.

**Results:** 17 pts with MSI-H tumors were identified (16 treated with pembrolizumab and 1 with dnravulumab). Its characteristics were: males (10, 59%), age (median 53.7 years, range 33–78), BRAF mutant (6, 35%), right sided (11, 65%), and liver-sparing (8, 47%). 7 (41%) had an objective response, 2 (12%) had stable disease. The median PFS was 9.97 months (mo), and the 6 and 12 mo PFS rates were 53% and 35%, respectively. TMB was available for 9 MSI-H cases (range 8–73 mutations/Mb): 1 CR (TMB 73), 1 PR (TMB 71), and 1 SD (TMB 31), and 6 PD (TMB: 6.13, 16, 18, 25, 36). We categorized our patients based on the lowest 10% (TMB < 23.5) and 25% (TMB < 33.06) TMB cut points identified from a large Foundation Medicine database of MSI-H MCRC. All 4/4 patients in the lowest TMB decade and 5/6 in the lowest TMB quartile experienced PD. On univariate analysis, only hepatic metastases (p = 0.01) and low TMB (p = 0.02) were associated with poor PFS.

**Conclusions:** A substantial percentage of pts with MSI-H tumors will progress with PD-1/PD-L1 inhibitors; these patients appear to be enriched for a low TMB status and hepatic metastases. Additional studies should explore TMB as a predictive marker of response to checkpoint inhibition in MSI-H CRC.

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