Background Immunosuppressive myeloid cells in the tumor microenvironment (TME) limit the efficacy of immune checkpoint inhibitors (ICIs) in head and neck squamous cell carcinoma (HNSCC). Preclinical and clinical studies demonstrated that antibody blockade of semaphorin 4D (SEMA4D) reverses immunosuppression, including attenuation of MDSC recruitment and function and promotes organization of lymphoid aggregates within tumors, leading to enhanced efficacy of ICIs. Pepinemab, a SEMA4D blocking antibody, in combination with avelumab was well tolerated and provided clinical benefit in patients with ICi-resistant, PD-L1-low NSCLC. The primary hypothesis of this proof-of-concept study is that pepinemab in combination with pembrolizumab will improve the efficacy of immunotherapy in R/M HNSCC.

Methods KEYNOTE-B84 (NCT04815720) is an ongoing single-arm open-label study evaluating the safety, efficacy, and PK/PD of pepinemab in combination with pembrolizumab as first-line treatment of R/M HNSCC. The study includes immunotherapy naïve patients who have tumor PD-L1 combined positive scores (CPS) of <20 and ≥20 with an interim analysis when 36 patients complete the first tumor response assessment. The primary efficacy endpoint is ORR, and secondary endpoints include PFS, DoR, and OS, as well as exploratory biomarker analyses. Pre- and on-treatment biopsies are collected for evaluation of immune contexture in TME. Data presented here include pre-specified interim analysis of safety, efficacy, and biomarker assessments.

Results The combination appears to be well tolerated with no DLTs observed or safety signals identified by the SMC. Notably, in the PD-L1 low population (CPS<20, N=19), we observed approximately a doubling in ORR, DCR, and PFS compared to reported single agent pembrolizumab. Among the CPS<20 population, ORR was 21.1% (2 CR and 2 PR), DCR was 73.7%, and median PFS was 5.7 months. In contrast, in the CPS>20 subgroup, the ORR was 17.6% (n=17), similar to ICI monotherapy for this population. Spatial multiplex IHC analysis of pre- and post-treatment tumor biopsies demonstrated an increase in activated APC, reduced recruitment of MDSC, and highly organized immune aggregates (figure 1) that corresponded with disease control.

Conclusions The pre-specified interim analysis of the ongoing KN-B84 study showed that pepinemab in combination with pembrolizumab was well-tolerated, suggested early signs of improved anti-tumor response over single agent pembrolizumab in the difficult to treat PD-L1 low group, and provided evidence of treatment-induced biomarker changes in the TME of responder tumors, including formation of high-density lymphoid aggregates.

REFERENCES