Background Semaphorin4D (SEMA4D) regulates immune cell infiltration and suppressive features of myeloid cells in the tumor via engaging with receptors, PLXNB1/2 and CD72. In preclinical and clinical studies, SEMA4D blockade enhances efficacy of immune checkpoint blockade (ICB) by invigorating lymphocyte infiltration and limiting suppressive myeloid cell properties in tumors. We hypothesized pepinemab (a SEM4D-blocking Ab), when combined with ICB, enhances crosstalk between B and T cells present as part of tertiary lymphoid structures (TLS) within the tumor microenvironment (TME) of melanoma patients.

Methods Consenting patients with resectable stage III melanoma received standard-of-care, neoadjuvant nivolumab alone, pepinemab/nivolumab, pepinemab/ipilimumab, or pepinemab/nivolumab/ipilimumab (NCT03769155). Following six weeks of therapy, patients underwent surgical resection. Patients also provided peripheral blood draws pre-treatment, two weeks into treatment, and at time of surgery. Surgical tissue and blood underwent high dimensional immune analysis using 32-color flow cytometry. Pretreatment archival tissue was also used in conjunction with on study surgical resection tissue to evaluate spatial distribution of immune populations using multiplex immunohistochemistry and Nanostring CosMx single cell imaging. Surgical resection tissue and matched blood was used for TCR and BCR sequencing.

Results Our work reveals that neoadjuvant combination treatments were well tolerated and resulted in pathologic and durable clinical responses. Moreover, patients given pepinemab/nivolumab/ipilimumab have not experienced tumor recurrence after treatment; more than 2 years later (ongoing response in 8/8 patients). Pepinemab in combination with nivolumab (either alone or with ipilimumab) significantly increased tumor-infiltrating B cells (CD19+), and CD4+ T cells within surgical tissue, compared to surgery or nivolumab alone. An increase in the frequency of CD4+ T cells that expressed the novel costimulatory molecule CD26 was also detected in responsive patients. Multiplex IHC revealed that pepinemab with nivolumab (alone or with ipilimumab) led to generation of tertiary lymphoid structures (TLS) comprised of B cells and T cells within the tumor bed. More tumor-infiltrating B cells and CD4+CD26hi T cells were associated with clinical response in patients receiving pepinemab and nivolumab (with or without ipilimumab). An increase in TCR and BCR clonal diversity was observed in tumors from patients receiving pepinemab-containing regimens, as compared to those receiving nivolumab alone. Nanostring CosMX transcriptomic analysis will be updated at presentation.

Conclusions Pepinemab in combination with nivolumab and ipilimumab robustly modulates immune responses in tumors from patients with resectable metastatic melanoma. Given the encouraging clinical activity and tolerability of these regimens, future studies should evaluate the use of pepinemab combined with ICB in other tumor indications.

Trial Registration NCT03769155

References