Background Semaphorin 4D (SEMA4D) modulates suppressive myeloid cells to promote infiltration of effector immune populations into the tumor microenvironment (TME). When combined with immune checkpoint blockade (ICB), SEMA4D blockade limits tumor progression in preclinical models. We have shown that pepinemab (a SEM4D-blocking Ab) can be safely combined with ICB in the neoadjuvant setting, and we hypothesize it will enhance immune infiltration in TME and benefit patients with resectable stage III melanoma.

Methods Patients with resectable stage III melanoma received neoadjuvant nivolumab alone, pepinemab/nivolumab, pepinemab/ipilimumab, or pepinemab/nivolumab/ipilimumab for six weeks followed by surgical resection (NCT03769155). A control cohort underwent surgery without neoadjuvant therapy. Full clinical data from this trial will be presented at ESMO 2022. Peripheral blood was drawn at three time points: a) pre-treatment, b) two weeks into treatment, and c) at time of surgery. High dimensional immune analysis was performed on tissue and blood 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. Finally, pharmacodynamics of SEMA4D blockade by pepinemab was tested using flow-based saturation assays.

Results Pepinemab treatment significantly increased tumor-infiltrating B cells (CD19+) and CD4+ T cells in surgical tissue of patients also given nivolumab (alone or with ipilimumab). A striking increase in a sub-population of proliferating (Ki67+) CD4+ T cells expressing the costimulatory molecule CD26 was also detected in patients receiving pepinemab-containing regimens (as compared to those receiving nivolumab alone). Intriguingly, tertiary lymphoid structures (TLS) comprised of a rich density of B and T cells were found in the tumor bed of patients given the tripartite therapy, as illuminated by spatial distribution of these immune populations using multiplex IHC. Patients experiencing a major pathologic response to pepinemab and nivolumab (with or without ipilimumab) had increased frequencies of tumor-infiltrating B cells and CD4+CD26hi T cells and elevated M1/M2 macrophage ratio. Multiplex IHC results, biomarker analysis, and peripheral blood analysis will be updated at presentation.

Conclusions Neoadjuvant pepinemab with nivolumab (alone or with ipilimumab) modulates immune responses in tumors from patients with resectable melanoma, particularly those with major pathologic responses. Mechanistically, this therapy may act in part by fostering interactions between B and T cell populations within TLS in tumors, with concurrent modulation of myeloid cells. Given the encouraging clinical activity and tolerability of these regimens, the addition of pepinemab has the potential to augment the activity of ICB in advanced melanoma.

Trial Registration Information regarding this clinical trial is available at www.clinicaltrials.gov, NCT03769155.