

SEMA4D Blockade Reshapes the Tumor Immune Environment in Neoadjuvant Melanoma Study

Nature Communications publication provides new evidence that Vaccinex's pepinemab may help reshape the tumor environment to support a coordinated immune attack on cancer, potentially complementing checkpoint inhibitors and other immunotherapies

ROCHESTER, N.Y., October 6, 2026 (GLOBE NEWSWIRE) -- Vaccinex, Inc. A clinical-stage biotechnology company pioneering a differentiated approach to treating cancer and Alzheimer's disease (AD) through the inhibition of Semaphorin 4D (SEMA4D), today announced the publication in *Nature Communications* of results from an Emory University and Winship Cancer Institute-sponsored pilot study evaluating pepinemab in patients with melanoma. The publication represents an important milestone in an almost decade-long scientific partnership between Vaccinex and Winship investigators, focused on advancing the understanding of SEMA4D biology and its potential application in cancer immunotherapy. The findings provide new evidence in human cancers supporting Vaccinex's strategy of targeting SEMA4D to reshape the tumor immune environment and promote conditions that support recognition of cancer cells and a coordinated antitumor immune response that may complement checkpoint inhibitors and other immunotherapies.

The study evaluated pepinemab in combination with the checkpoint inhibitors nivolumab and/or ipilimumab before surgery in patients with resectable metastatic melanoma. Consistent with its biomarker-driven design, the study focused on measuring treatment-associated changes in tumor immunity. The predefined primary biomarker endpoint was met; the trial was not powered to establish clinical efficacy.

Researchers found that pepinemab-containing regimens were associated with broad changes in the tumor microenvironment consistent with enhanced antitumor immunity. These changes included stronger biomarker signals associated with tumor recognition and antigen presentation, recruitment and activation of immune cells, and the development of highly organized immune structures known as mature lymphoid aggregates.

Importantly, greater abundance of mature lymphoid aggregates was associated with longer recurrence-free survival. This observation provides an encouraging link between the immune remodeling identified in the study and patient outcomes; however, the small biomarker-focused trial was not designed to demonstrate a clinical benefit from pepinemab. Confirmation in larger, randomized studies will be needed.

The publication, "Neoadjuvant pepinemab in combination with nivolumab and/or ipilimumab in resectable metastatic melanoma: a pilot biomarker-driven trial," is the result of a longstanding scientific collaboration between Vaccinex and investigators at Winship Cancer Institute of Emory University led by Michael C. Lowe, MD, MA, Gregory B. Lesinski, PhD, MPH, and Chrystal M. Paulos, PhD with additional contributions from The University of Texas MD Anderson Cancer Center led by Jennifer Wargo, MD, MMSc. The investigator-initiated trial was sponsored by Emory University and Winship Cancer Institute, with Vaccinex providing pepinemab together with scientific and research support.

Key Findings

1. **Pepinemab was associated with broad remodeling of the tumor immune environment.**

SEMA4D blockade was associated with changes across several components of antitumor immunity, including biological programs involved in antigen presentation, immune-cell recruitment and activation, together with changes in myeloid cells that can influence whether the tumor environment suppresses or supports an immune response.

2. **Pepinemab-containing regimens were associated with highly organized immune structures within tumors.**

Mature lymphoid aggregates contained distinct populations of immune cells arranged in defined regions that enable local immune interactions. Some aggregates displayed features resembling tertiary lymphoid structures (TLS), specialized sites where multiple components of an immune response can come together within or near tumors.

3. **More mature immune structures were associated with longer recurrence-free survival.**

Patients with greater abundance of mature lymphoid aggregates tended to remain recurrence-free longer. Additional analyses found evidence of expanded T- and B-cell populations within these structures, supporting the concept that they represented sites of active immune responses. Because the trial was designed to study biological effects and included a relatively small number of patients, these clinical associations are exploratory and require confirmation in larger studies.

About the Study

The investigator-sponsored pilot trial (NCT03769155) evaluated pepinemab in combination with nivolumab and/or ipilimumab in patients with resectable metastatic melanoma. Patients received two doses of treatment before planned surgery, allowing investigators to directly examine how the treatments affected the immune environment within subsequently resected tumors.

Thirty-eight patients participated in the study, and neoadjuvant treatment did not prevent or postpone curative-intent surgical resection. No grade 4 or 5 adverse events occurred during treatment before or after surgery.

The trial represents one component of a scientific partnership between Vaccinex and Winship Cancer Institute of Emory University, advancing SEMA4D research from mechanistic studies toward clinical evaluation in cancer. Vaccinex supplied pepinemab and supported multiple aspects of the research program, including scientific and operational oversight, generation and analysis of study data, and development of the scientific publication. Bristol Myers Squibb provided nivolumab and ipilimumab.

Together, these findings provide evidence from human tumors supporting the proposed mechanism of pepinemab and Vaccinex's strategy of targeting SEMA4D as a means of reshaping the tumor immune environment. By promoting conditions associated with improved antigen presentation, immune-cell recruitment and organized adaptive immunity, SEMA4D blockade may offer a complementary approach to checkpoint inhibition and other cancer immunotherapies. The results support continued evaluation of pepinemab-containing combinations in melanoma and other solid tumors.

Publication

Ruffin, A.T., Mallow, C.L., Olson, B.M. *et al.* Neoadjuvant pepinemab in combination with nivolumab and/or ipilimumab in resectable metastatic melanoma: a pilot biomarker-driven trial. *Nat Commun* (2026). <https://doi.org/10.1038/s41467-026-78231-3>

Clinical trial: NCT03769155

About Pepinemab

Pepinemab is a humanized IgG4 monoclonal antibody designed to block SEMA4D, which can otherwise bind to plexin-B1 receptors to trigger collapse of the actin cytoskeleton in cells and lead to loss of homeostatic functions of astrocytes and other glial cells in the brain and of dendritic cells in immune tissue. Pepinemab appears to be well-tolerated with a favorable safety profile in multiple clinical trials in different neurological and cancer indications.

About Vaccinex Inc.

Vaccinex, Inc. is pioneering a differentiated approach to treating slowly progressive neurodegenerative diseases and cancer through the inhibition of semaphorin 4D (SEMA4D). The Company's lead drug candidate, pepinemab, blocks SEMA4D, a potent biological effector that it believes triggers damaging inflammation in chronic diseases of the brain and prevents infiltration and activation of immune cells in tumors. Pepinemab is being studied as a monotherapy in the Phase 2b SIGNAL-AD2 study in Alzheimer's Disease, and the Company has previously published promising Phase 2 data in Huntington's disease. In oncology, pepinemab is being evaluated in combination with KEYTRUDA® in the Phase 1b/2 KEYNOTE-B84 study in recurrent or metastatic head and neck cancer (HNSCC). The oncology clinical program also includes several investigator-sponsored studies in solid tumors including breast cancer and melanoma. Vaccinex has global commercial and development rights to pepinemab and is the sponsor of the KEYNOTE-B84 study which is being performed in collaboration with Merck Sharp & Dohme Corp, a subsidiary of Merck and Co, Inc. Kenilworth, NJ, USA. Additional information about the study is available at: clinicaltrials.gov. KEYTRUDA is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA.

Forward Looking Statements

To the extent that statements contained in this press release are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited to, statements about expectations and objectives with respect to the results and timing of the SIGNAL-AD clinical trials; our plans, expectations and objectives with respect to the results and timing of the SIGNAL-AD and KEYNOTE-B84 clinical trials; the use and potential benefits of pepinemab in R/M HNSCC, lung cancer, metastatic pancreatic adenocarcinoma (PDAC) and other indications; the potential for benefits as compared to single agent KEYTRUDA® or BAVENCIO®; expectations with respect to the collaboration of Merck; and other statements identified by words such as "anticipate," "believe," "plans," "schedule," "being," "will," "appears," "expect," "ongoing," "potential," "promising," "suggest", and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of our research and pre-clinical development programs, clinical development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties inherent in the execution, cost and completion of preclinical studies and clinical trials, that interim and preliminary data may not be predictive of final results and does not ensure success in later clinical trials, uncertainties related to regulatory approval, risks related to our dependence on our lead product candidate pepinemab, and other matters that could affect our development plans or the commercial potential of our product candidates. Except as required by law, the Company assumes no obligation to update these forward-looking statements. For a further discussion of these and other factors that could cause future results to differ materially from any forward-looking statement, see the section titled "Risk Factors" in our periodic reports and the other risks and uncertainties described in the Company's annual year-end filings.

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