Pepinemab – Anti-SEMA4D Antibody for Neurodegenerative Disease and Cancer Immunotherapy

VACCINEX

Unique Targets
Novel Mechanisms
New Medicines

Corporate Presentation

January 2023

VCNX

Forward Looking Statements

To the extent that statements contained in this presentation 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 the Company's plans, expectations and objectives with respect to the results and timing of clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Head and Neck cancer, Huntington's and Alzheimer's disease and other indications, and other statements identified by words such as "may," "will," "appears," "expect," "planned," "anticipate," "estimate," "intend," "hypothesis," "potential," "advance," 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 the Company's 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 and clinical trials, uncertainties related to regulatory approval, the risks related to the Company's dependence on its lead product candidate pepinemab, the ability to leverage its ActivMAb® platform, the impact of the COVID-19 pandemic, and other matters that could affect the Company's development plans or the commercial potential of its 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 the Company's periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in the Company's most recent year end Annual Report on Form 10-K and subsequent filings with the SEC.

Lead Product: Pepinemab

❖ **Novel Mechanistic Approach**	First-in-class immunotherapy targeting Semaphorin4D Regulates inflammatory processes that exacerbate disease pathology
❖ **Broad application**	Neuro-immunology: Huntington's Disease, Alzheimer's Disease, etc Immuno-Oncology
❖ **Favorable safety and tolerability**	**Well-tolerated in >400 patients** Non-invasive route of administration: Intravenous infusion
❖ **Clinical Proof of Concept**	**Neurology** • Target engagement in brain • Documented **improvements in cognitive function** and brain **metabolic activity** in Huntington's Disease **Oncology** • Enhances activity but does <u>not</u> enhance toxicities of immune checkpoint inhibitors • Demonstrated **clinical benefit in refractory/resistant cancers**
❖ **In-house expertise and partnerships to realize value**	alzheimer's association Alzheimer's Drug Discovery Foundation MERCK Merck, MSD Merck, KGaA Darmstadt

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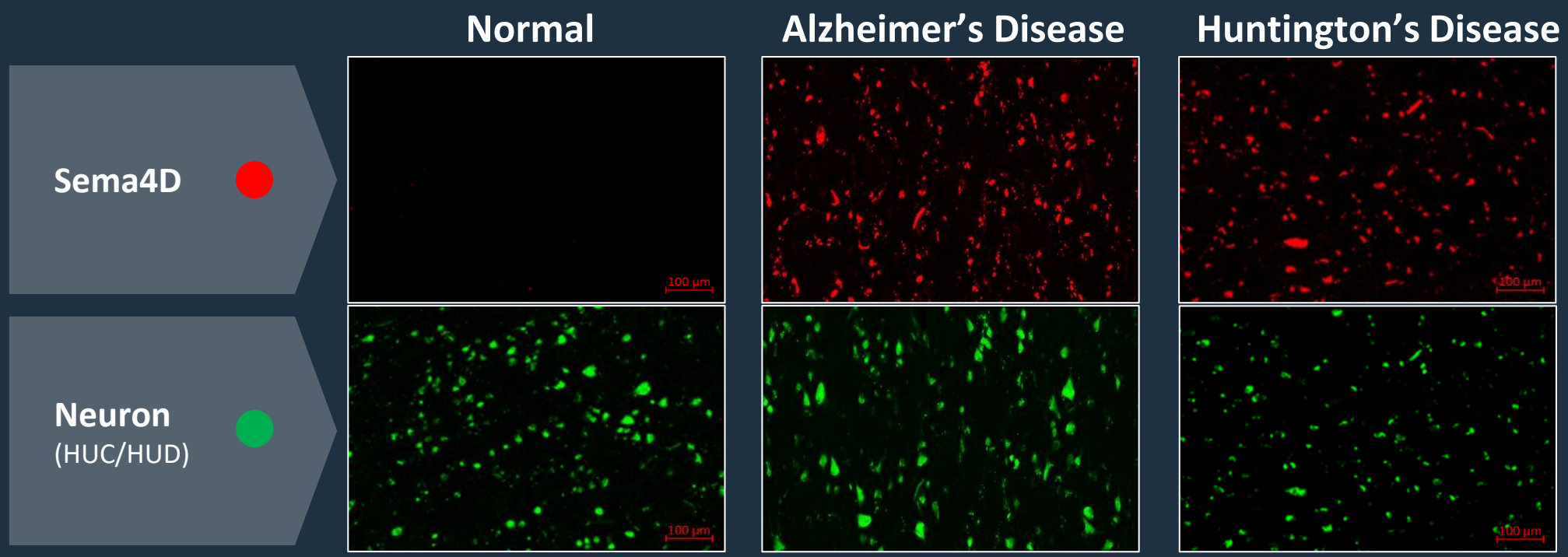
Pepinemab Antibody for treatment of Neurodegenerative Disease

A novel mechanism of action with broad application in emerging neuro-immunology field

Demonstrated favorable clinical safety and proof of concept

SEMA4D IS OBSERVED TO BE UPREGULATED IN NEURONS DURING DISEASE PROGRESSION

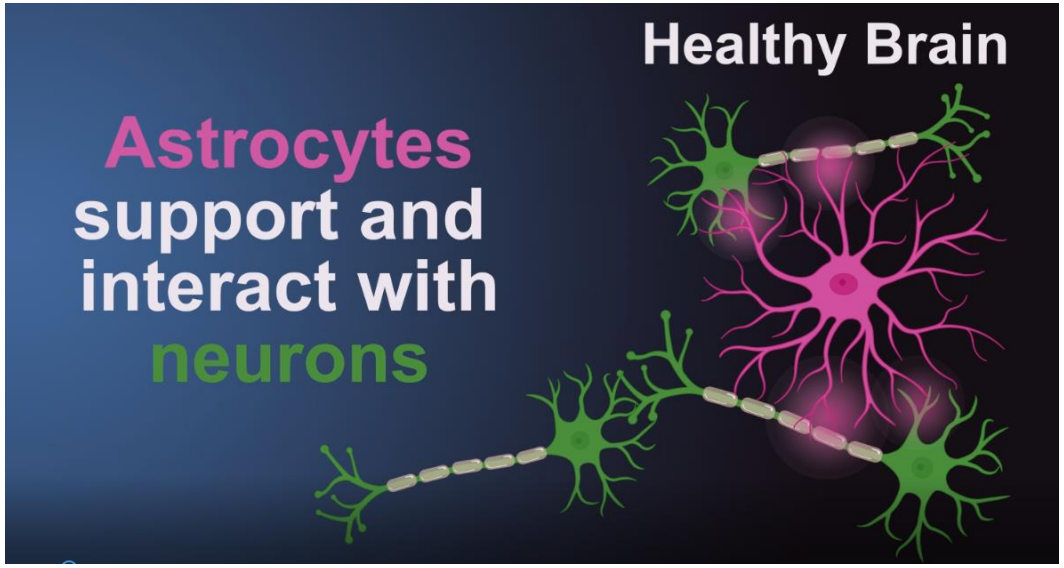


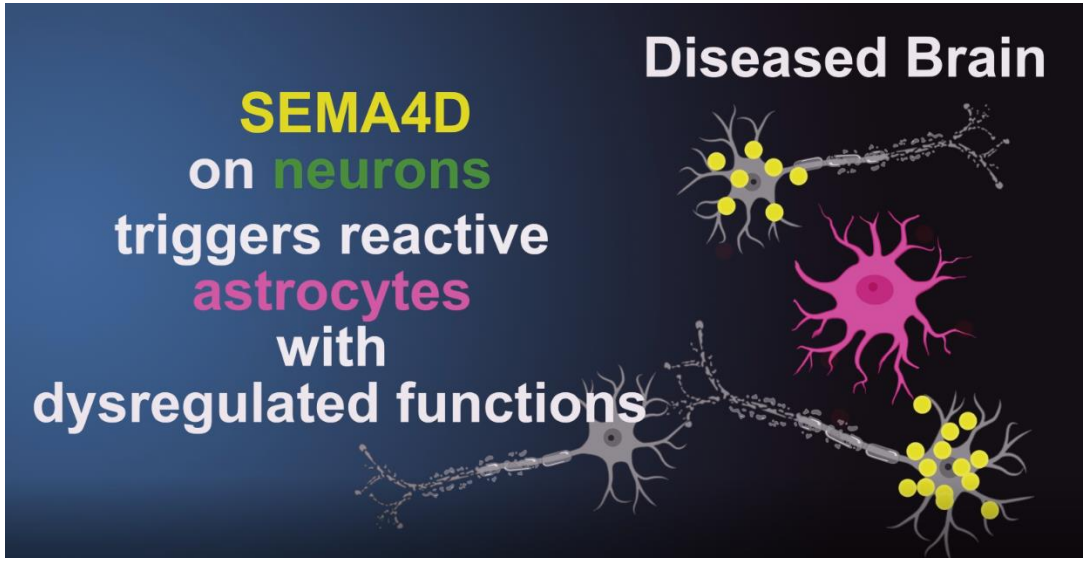
Human autopsy sections of frontal lobe

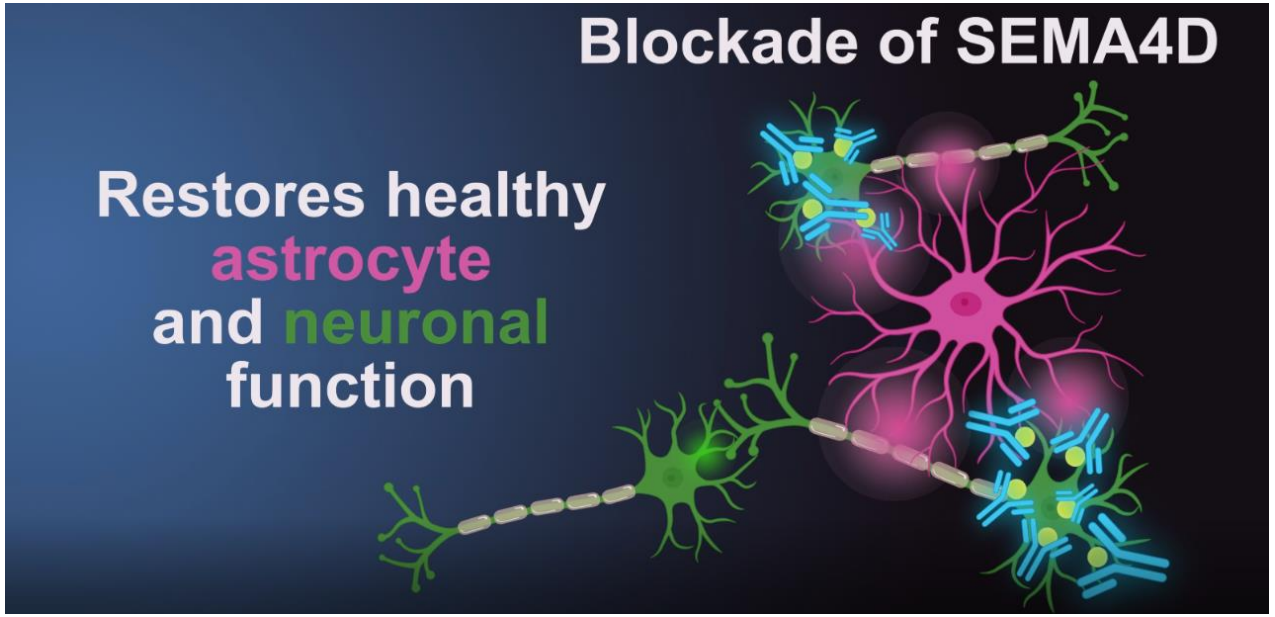
Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity
Elizabeth E Evans, Vikas Mishra, Crystal Mallow, Elaine Gersz, Leslie Balch, Alan Howell, Ernest S. Smith, Terrence L. Fisher, Maurice Zauderer*
Journal of Neuroinflammation, 2022,.

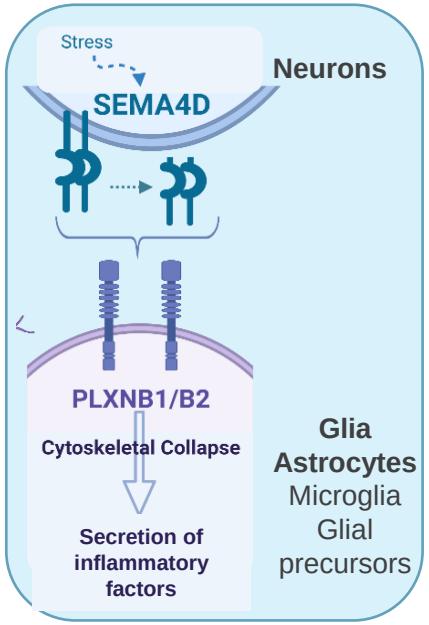
VACCINEX

SEMA4D regulates neuron-astrocyte communication









PEPINEMAB FOR NEURO-IMMUNOLOGY

2 key publications in 2022

Clinical Experience in HD

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01919-8

Check for updates

OPEN

Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial

Andrew Feigin[1], Elizabeth E. Evans[2], Terrence L. Fisher[2], John E. Leonard[2], Ernest S. Smith[2], Alisha Reader[2], Vikas Mishra[2], Richard Manber[3], Kimberly A. Walters[4], Lisa Kowarski[4], David Oakes[5], Eric Siemers[6], Karl D. Kieburtz[5], Maurice Zauderer[2]✉ and the Huntington Study Group SIGNAL investigators*

Mechanism of Action

Evans *et al. Journal of Neuroinflammation* (2022) 19:200
https://doi.org/10.1186/s12974-022-02509-8

Journal of Neuroinflammation

RESEARCH Open Access

Check for updates

Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity

Elizabeth E. Evans[1], Vikas Mishra[1], Crystal Mallow[1], Elaine M. Gersz[1], Leslie Balch[1], Alan Howell[1], Christine Reilly[1], Ernest S. Smith[1], Terrence L. Fisher[1] and Maurice Zauderer[1,2*]

HUNTINGTON'S DISEASE

Genetic Disease
HD is caused by dominant mutation in a single gene.

Unmet need
No approved treatments to alter the course of Huntington's Disease.

~40,000 individuals
with manifest disease in US

>150,000 more
at risk of inheriting mutation

Symptoms
Cognitive impairment = most significant impact on daily life (FDA Voice of the Patient)

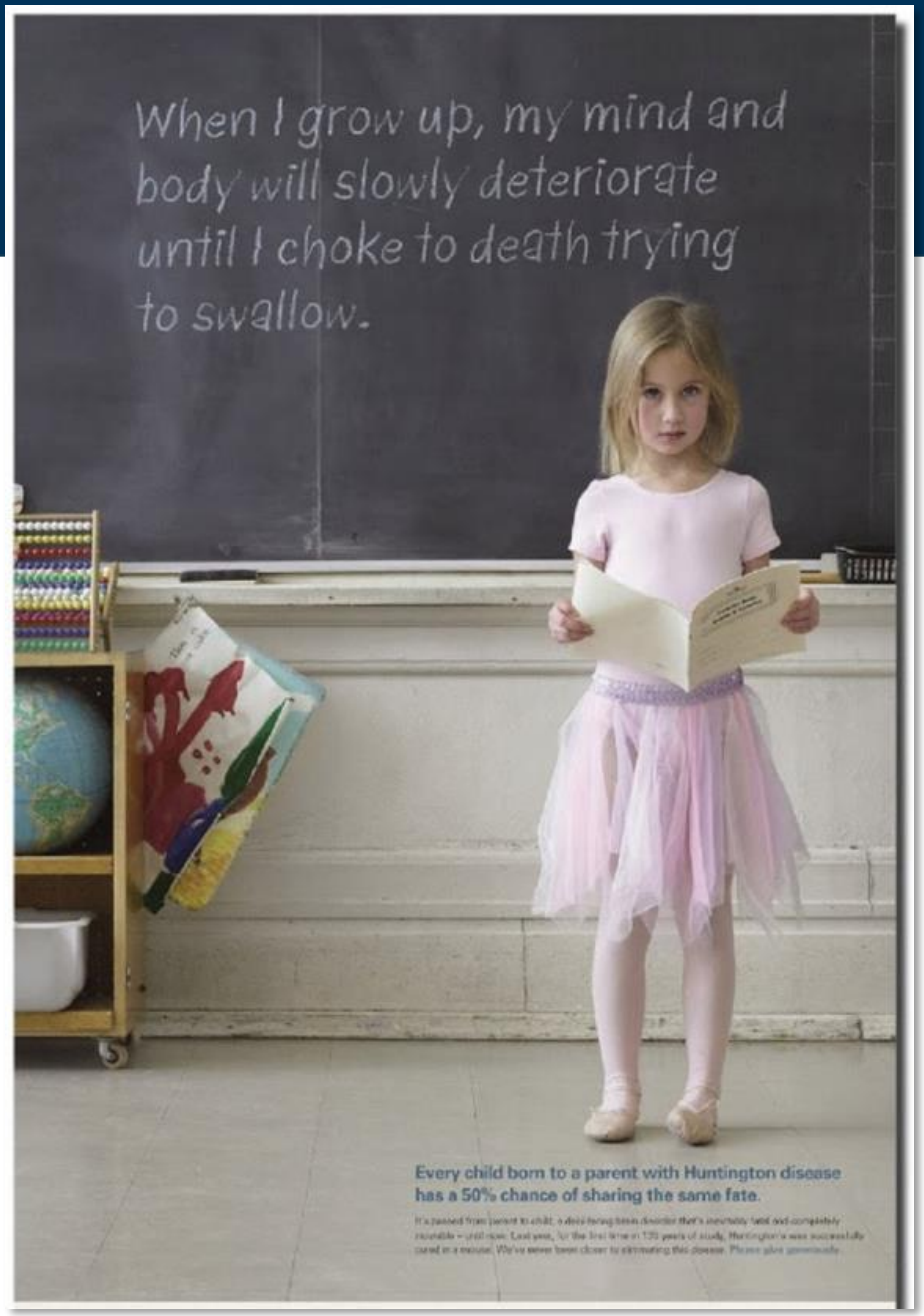


Photo credit: Huntington Society of Canada

HUNTINGTON'S DISEASE

Clinical Trial Design

SIGNAL

Orphan Disease and Fast Track Designations

Cohort B1 Early Manifest HD

n=179

CAG repeat ≥36
TFC 11-13, DCL 4

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Cohort B2 Late Prodromal HD

n=86

CAG repeat ≥36
DCL 2 or 3

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Data Analysis and Study Objectives

Safety and tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

Key Exploratory and Biomarker Outcomes
Brain Volume (vMRI)
Metabolic imaging (FDG-PET)

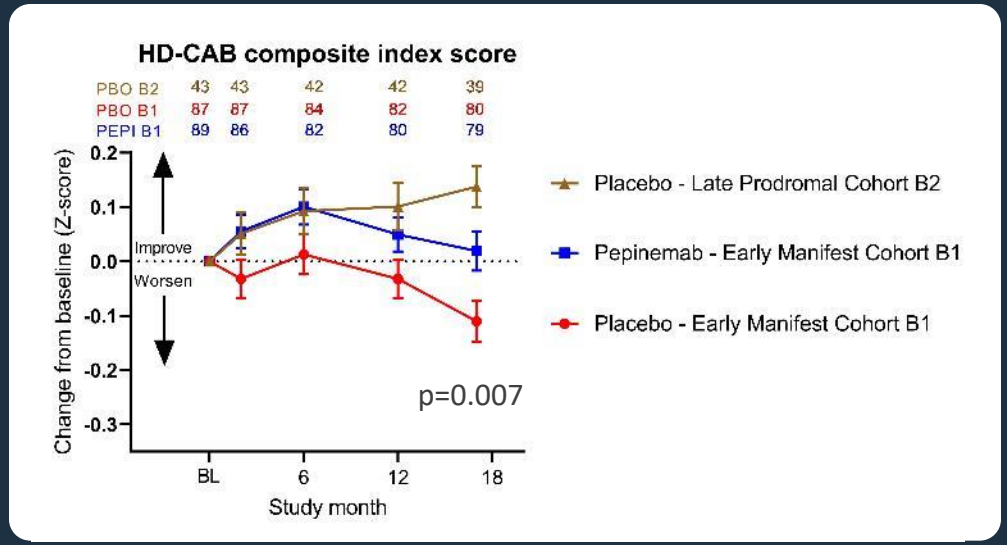
Post-hoc Subgroup Analyses

NCT02481674

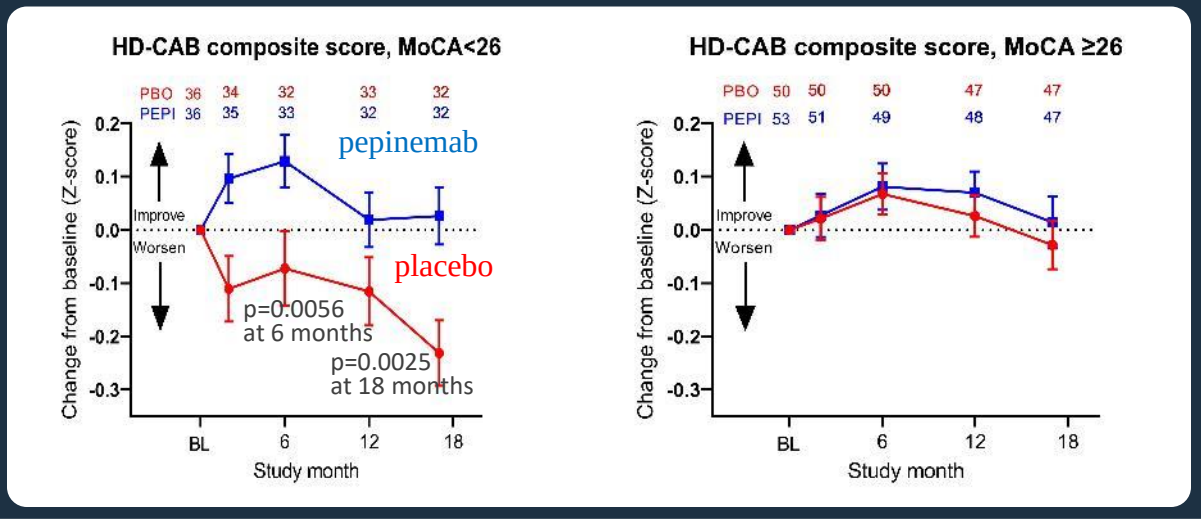
HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Exploratory and Post-hoc analysis

- "Learning effect" is lost when HD symptoms become manifest
- Pepinemab treatment restores the ability to benefit from experience (i.e., to learn)



- Treatment effect is most evident in patients with early signs of cognitive deficits (MoCA<26)



Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

FDG-PET CORRELATES WITH COGNITIVE FUNCTION

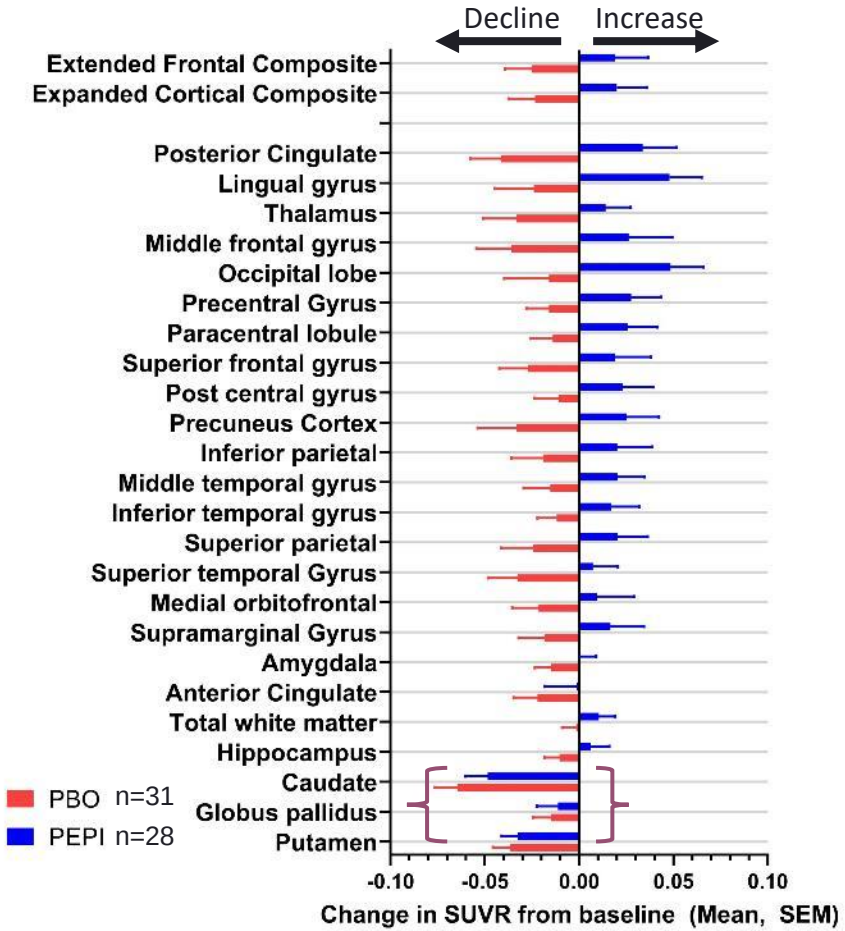
Pre-specified Exploratory Endpoint, Early Manifest cohort

1 FDG-PET measures brain metabolic activity.

2 Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.

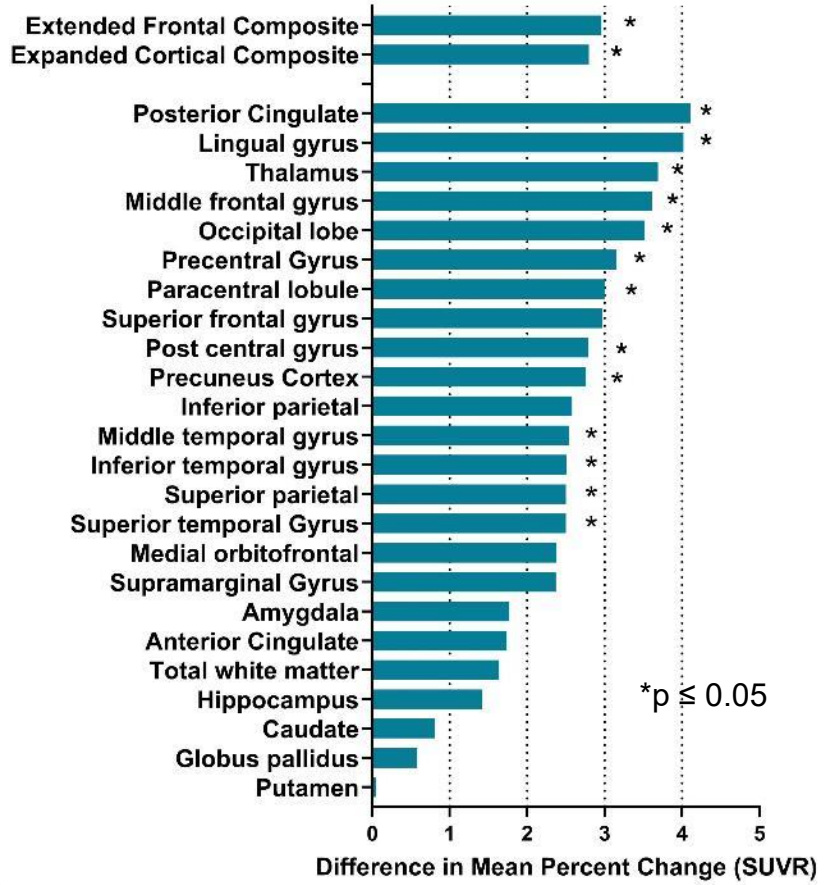
Pepinemab treatment appears to reverse loss of metabolic activity.

Change in FDG-PET at Month 18



SUVR = standardized uptake value ratio

Difference (PEPI-PBO) at Month 18



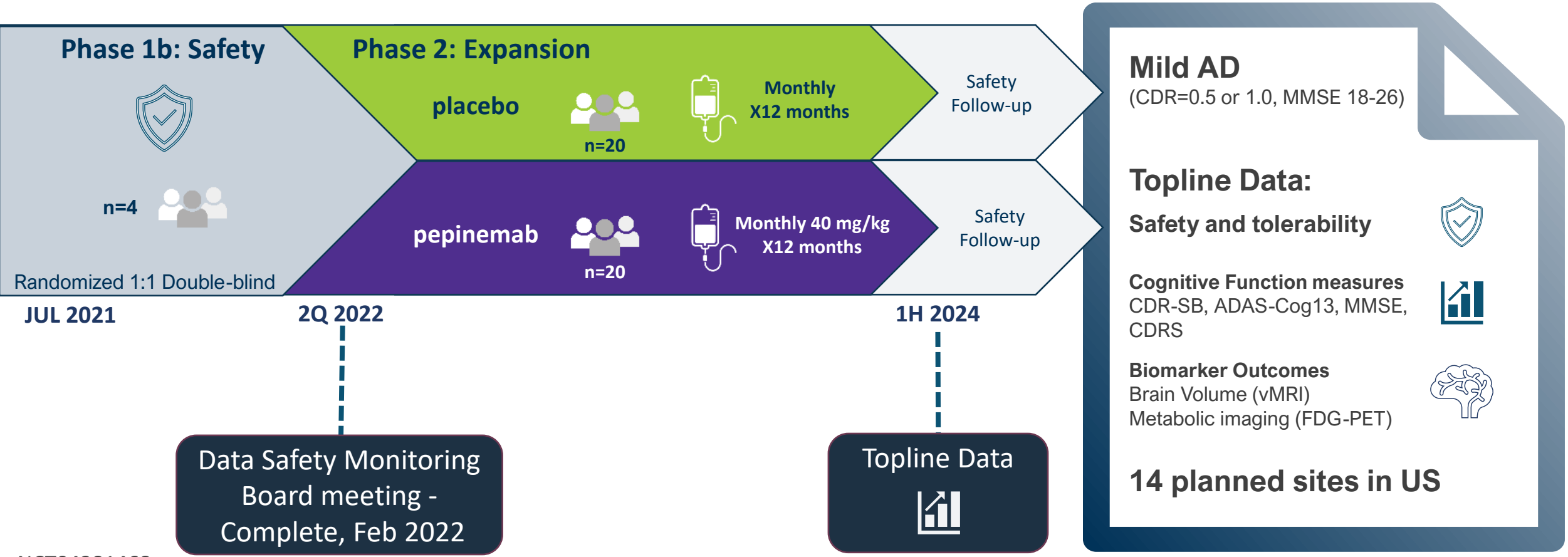
Feigin, A et al. *Nature Medicine* (2022)

ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

SIGNAL-AD

Funding by alzheimer's association® Alzheimer's Drug Discovery Foundation



NCT04381468

Pepinemab for Neuro-immunology

Well-tolerated

>300 patients dosed

AEs and discontinuation rates comparable to Placebo

Non-invasive route of administration

Intravenous, monthly dosing

Crosses blood brain barrier

Confirmed target saturation in CSF

Demonstrated clinical proof of concept

Improves cognition
(HD-CAB)

Improves brain metabolic activity
(FDG-PET)

Novel mechanism of action
Broad application

Demonstrated safety and activity in Huntington's Disease (~188K)

Ongoing Phase1/2 in Alzheimer's (~134M)
Potential application in Parkinson's, Primary Progressive MS, Rett Syndrome

Potential for **combination** therapy

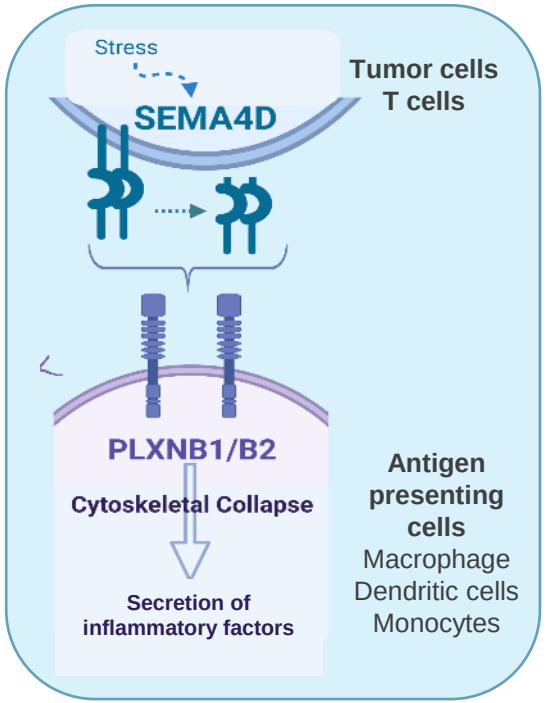
Pepinemab Antibody for Cancer Immunotherapy

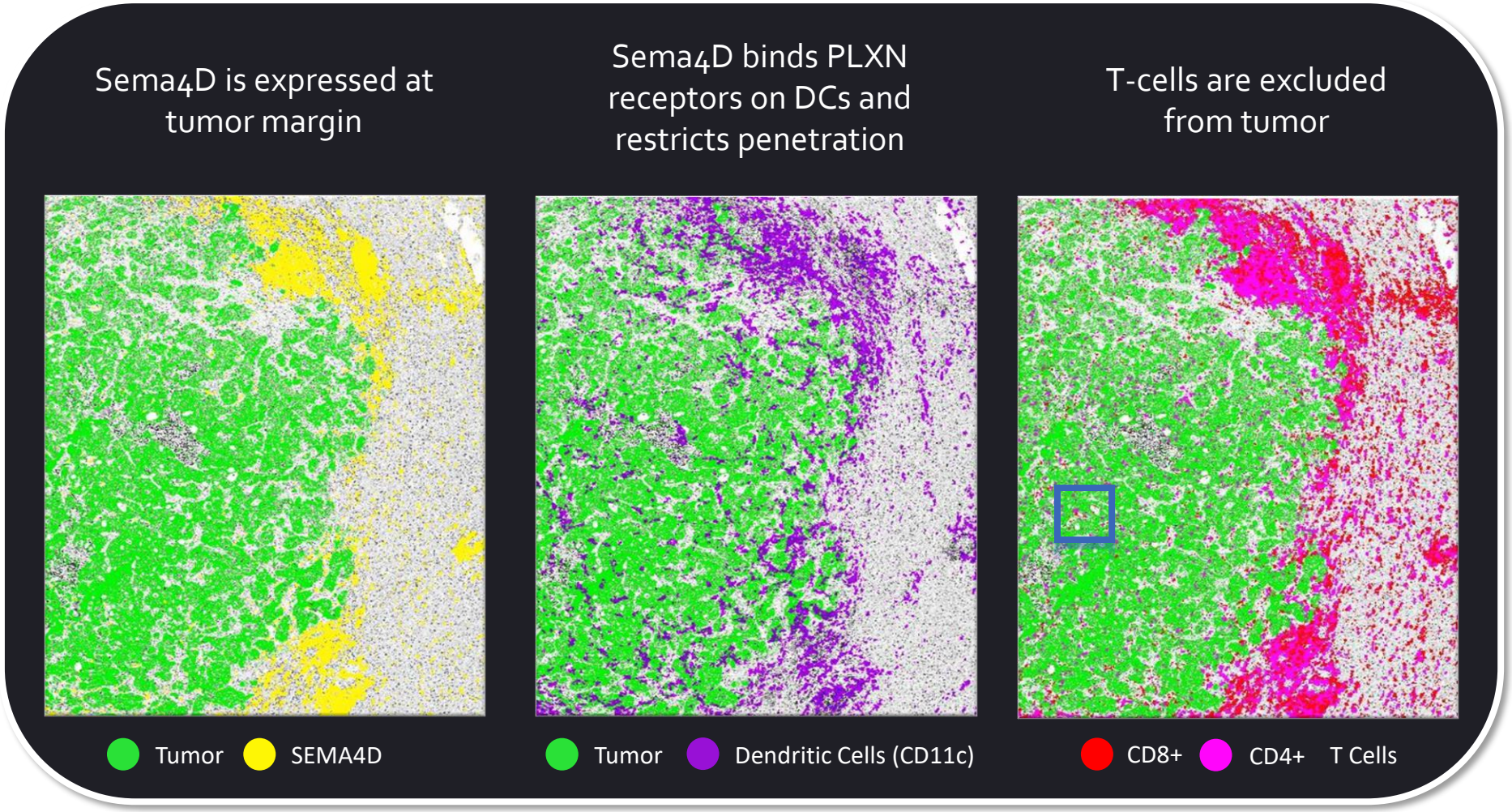
A novel mechanism of action that enhances activity but does not enhance toxicity of existing therapies when used in combination

WHY DOES IMMUNE RESPONSE FAIL IN TUMORS?

SEMA4D regulates

1. Immune Exclusion
2. Myeloid Suppression





Pro-inflammatory cells are excluded from tumor and build up at the invasive edge

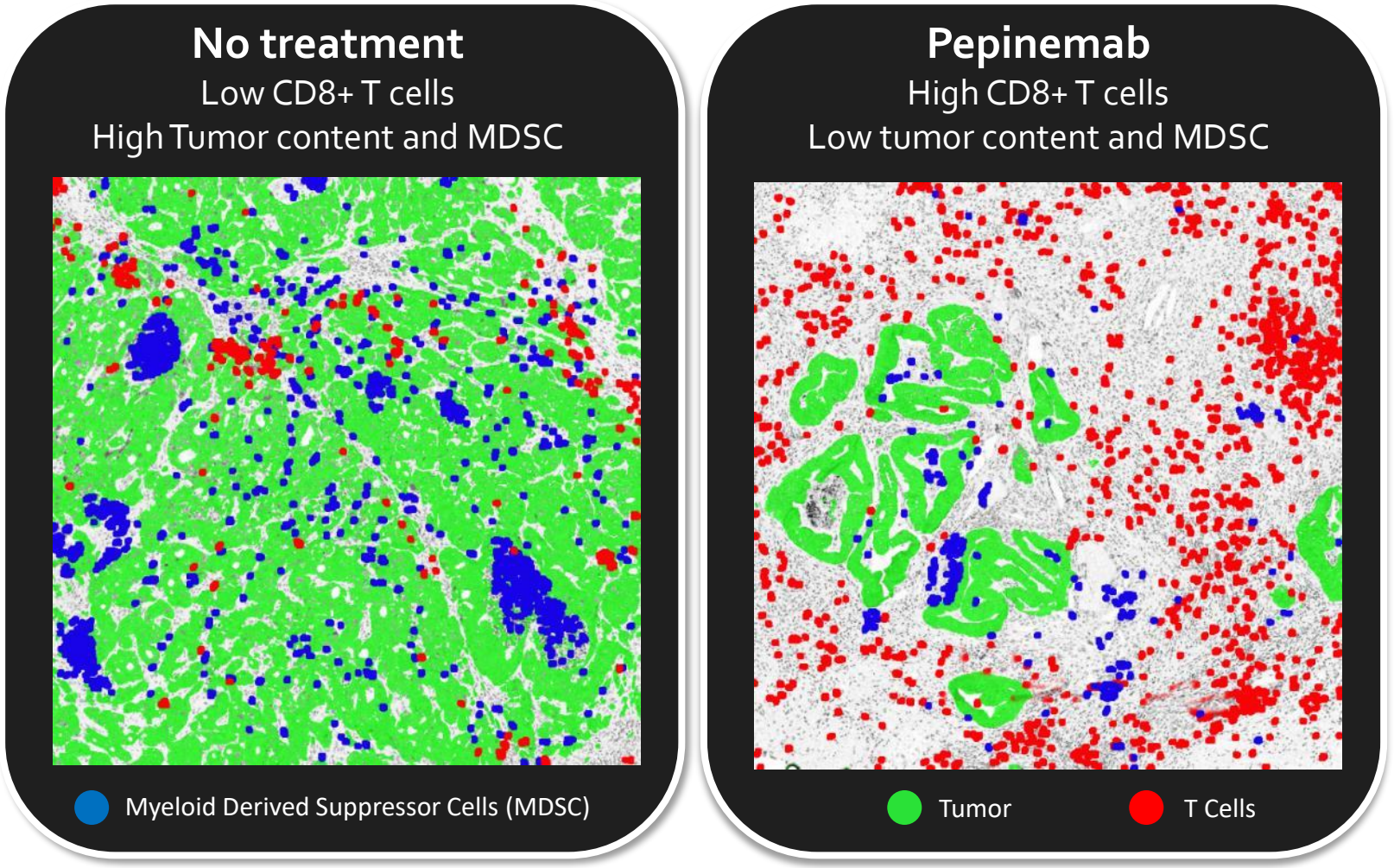
CD8 T cells align with Sema4D at the invasive edge of the tumor. Most of these excluded T-cells express Sema4D. Dendritic Cells express receptors for SEMA4D and are heavily excluded at the invasive edge.

Biopsy of Human metastatic colorectal tumor, in collaboration with Emory University (NCT03373188)

PEPINEMAB: UNIQUE MECHANISM

1 ↑ cytotoxic T cells

2 ↓ inhibitory suppressor cells

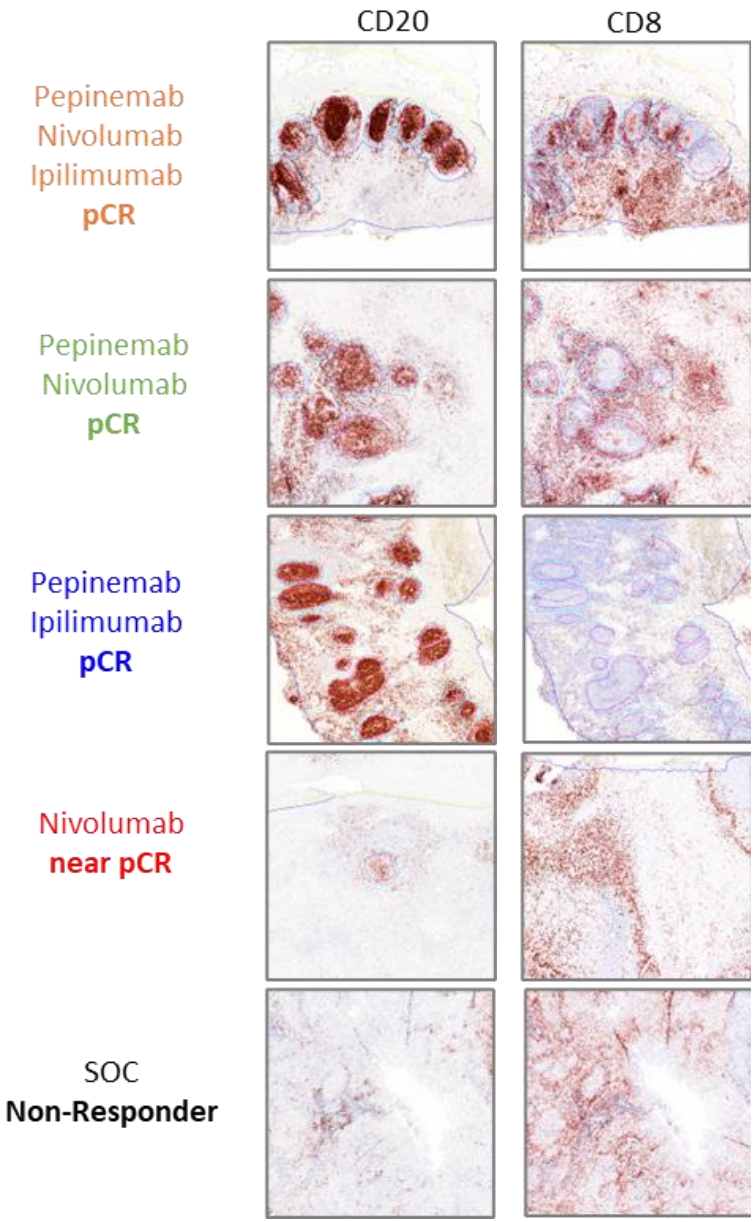


SEMA4D blockade reduces suppressive capacity of Myeloid Derived Suppressor Cells in the tumor.
Left: SEMA4D induces secretion of factors from myeloid suppressor cells that inhibit recruitment and activity of CD8 T cells.
Right: **Pepinemab treatment reverses inhibitory suppressive cells and facilitates T cell infiltration and activity.**

Biopsy of Human metastatic colorectal tumor, in collaboration with Emory University (NCT03373188)

PEPINEMAB: UNIQUE MECHANISM

PEPINEMAB:
Improved cellular communication through formation of organized lymphoid structures



CD20+ B cells in pepinemab Tx arms

CD20+ B cells and CD8+ T cells are ***organized*** in Pepi Tx arms

CD8 are not organized

Biopsies of Human melanoma tumors,
in collaboration with Emory University (NCT03769155), oral presentation at SITC, Nov 2022

Neoadjuvant immunotherapy trial
Integrated biomarker analysis

PARIS 2022 ESMO congress

VACCINEX

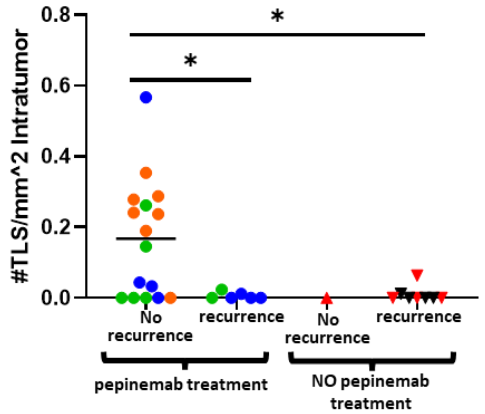
Sponsored by: EMORY WINSHIP CANCER INSTITUTE

Collaboration with: VACCINEX

Safety & Tolerability

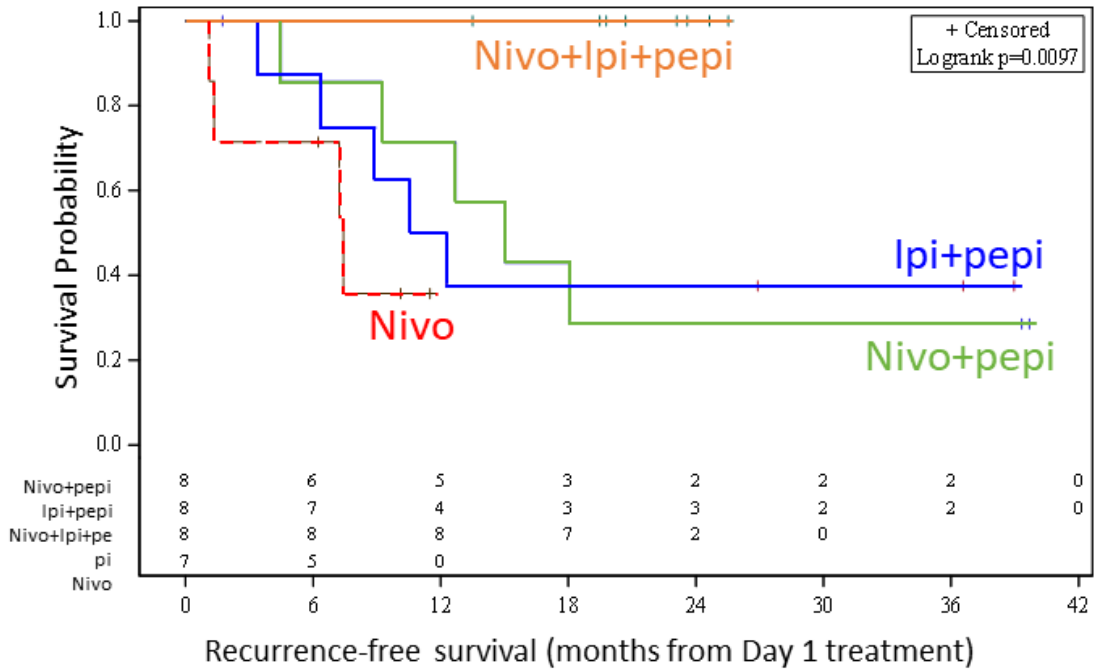
Pepinemab is well-tolerated and adds NO additional toxicity to PD-1 and CTLA-4 inhibitors in the **neoadjuvant setting**

Biomarker analysis



Formation of TLS correlates with RFS in melanoma patients

Recurrence-free Survival



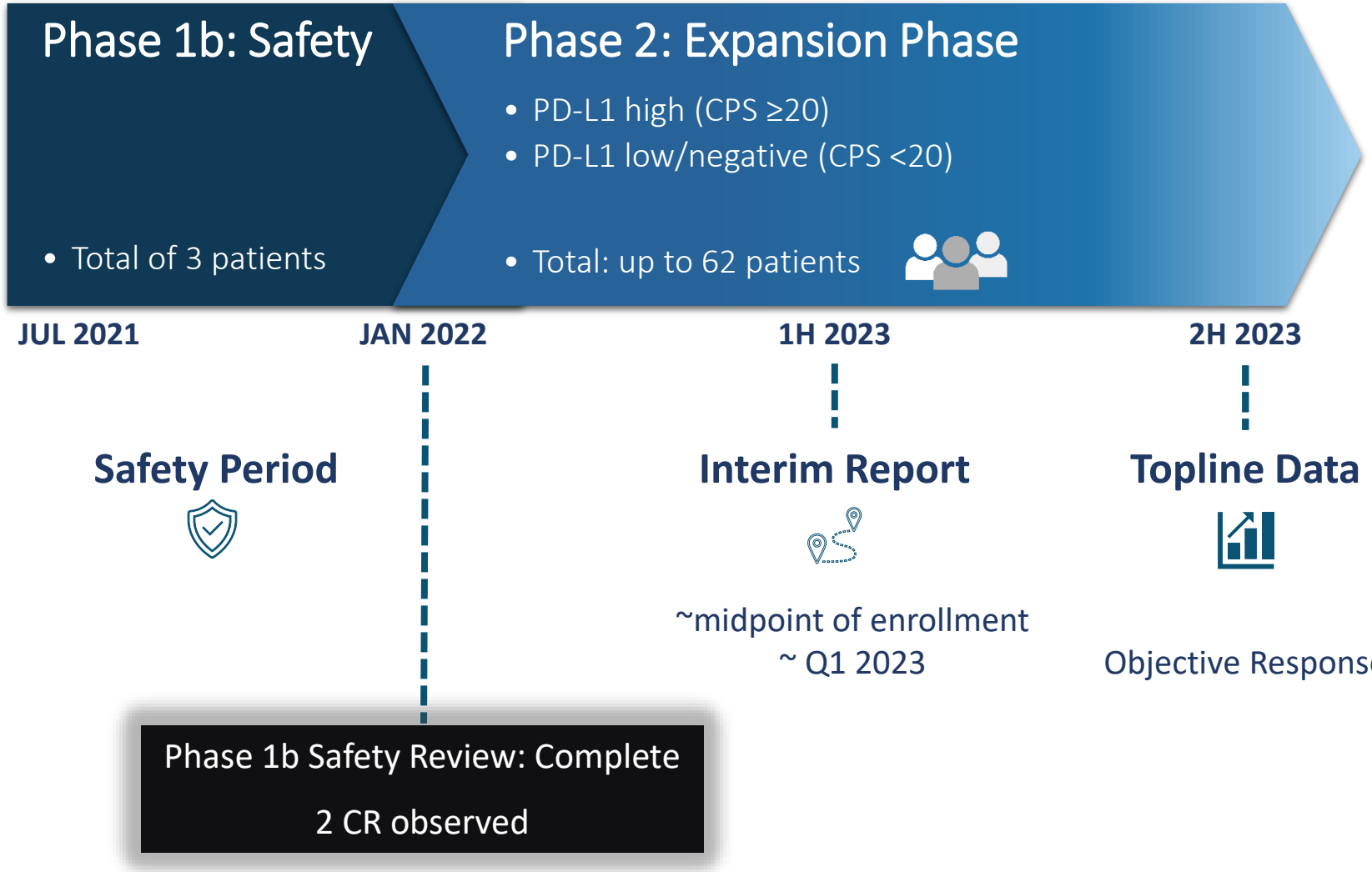
100% RFS
Triple combo

Delay of RFS
Double combos

(NCT03769155)
Oral abstract presentation by Dr. Michael Lowe at ESMO, Sep 2022
Biomarker analysis selected for oral presentation by Dr. Brian Olson at SITC, Nov 2022

KEYNOTE-B84 HEAD AND NECK CANCER TRIAL

- **All patients receive standard of care Keytruda®, plus pepinemab for first- line treatment of recurrent or metastatic head and neck cancer**
- Open-label, continuous monitoring
- KEYNOTE-048 for historical comparison – same inclusion / exclusion criteria
- 18 sites in USA now open
- Ph1b Safety: COMPLETE
  - Well tolerated
  - RP2D: 20mg/kg pepi and 200mg pembro, Q3W
- Ph2 Expansion: ENROLLING
  - 33 patients enrolled, as of Jan01



Pepinemab for Immuno-Oncology

Well-tolerated

Does **not** enhance toxicity of companion drug

Novel and Independent Mechanism of Action

↑ T cell penetration/ organization
↓immune suppression

Established PK/PD

Confirmed target saturation in adult and pediatric patients

Can accommodate schedule of companion drug

Demonstrated clinical activity in PD-L1 low = Unmet Need

~2-3X ↑ in ORR compared to single agent ICI in PD-L1 low NSCLC

2/3 CR in Phase1b segment of ongoing HNSCC trial

Strong rationale for combination therapy

Demonstrated safety and enhanced activity in combination with immune checkpoint therapy in Lung Cancer & Head and Neck cancer

Neoadjuvant treatment for Melanoma

Corporate Overview

■ Unique Targets ■ Novel Mechanisms ■ New Medicines

ACHIEVEMENTS AND MILESTONES

Publish Clinical Data for SIGNAL study in Huntington's Disease in *Nature Medicine* Publish mechanism of action paper for neurodegenerative diseases in *Journal of Neuroimmunology*	August 2022
Request End of Phase 2 meeting with FDA to discuss clinical development strategies in Huntington's disease	**1H 2023**
Expect topline data from randomized, double-blind, placebo-controlled Alzheimer's disease phase 1b/2a study	**1H 2024**
Presentation of mechanism of action and biomarker results from melanoma combination immunotherapy trial, in collaboration with Emory University. Publication expected in 2023	4Q 2022 **2023**
Completed safety run-in segment of Phase 1b/2 study of Pepinemab in Combination with Keytruda® in front line Head & Neck Cancer **Expect interim data and JSC meeting with Merck**	1Q 2022 **1H 2023**

Currently exploring pharma collaborations

PIPELINE and MILESTONES

Research/Preclinical	Phase 1	Phase 2	Phase 3	Partner/Funding	Milestone
Pepinemab Antibody Platform (anti-Semaphorin 4D Mab)				All Studies Sponsored by:	
Oncology					
Pepinemab COMBO with Avelumab in **Non Small Cell Lung Cancer**			CLASSICAL -Lung	VACCINEX Merck, KGaA Darmstadt	Complete, Published 2021
Pepinemab COMBO with Pembrolizumab in **Head and Neck Cancer**			KEYNOTE-B84	MERCK Merck, MSD	Ongoing **Next data 1H 2023**
Neurology					
Pepinemab in **Huntington's Disease** (Orphan Drug and Fast Track Designations)			SIGNAL		Complete, **Nature Medicine, Aug 2022**
Pepinemab in **Alzheimer's Disease**			SIGNAL-AD	alzheimer's association Alzheimer's Drug Discovery Foundation	Ongoing **Data 1H 2024**

CONTACT US

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Ernest Smith, PhD
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Appendix

Vaccinex Selected References, Oncology

1. Shafique MR, Fisher TL, Evans EE, Leonard JEE, Pastore DRE, Mallow CL, Smith E, Mishra V, Schroder A, Chin KA, Beck JT, Baumgart MA, Govindan R, Gabrial NY, Spira AI, Seetharamu N, Lou Y, Mansfield AS, Sanborn RE, Goldman JW, Zauderer M. **A Phase Ib/2 Study of Pepinemab in Combination with Avelumab in Advanced Non–Small Cell Lung Cancer**. Clin Cancer Res 2021, doi: 10.1158/1078-0432.CCR-20-4792
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Schematics created with BioRender.com

Vaccinex Selected References, Neurology

1. Feigin AS, Evans EE , Fisher TL, Leonard JE, Reader A, Wittes J, Oakes D, Smith ES, Zauderer M, and the Huntington Study Group SIGNAL investigators. **Pepinemab antibody blockade of SEMA4D in patients with early Huntington's Disease: a randomized, placebo-controlled, Phase 2 trial.** Nature Medicine, 2022 Aug 8;1-11. doi: 10.1038/s41591-022-01919-8.
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Vaccinex Leadership Team

Maurice Zauderer, Ph.D.	**Founder, President and Chief Executive Officer**. Formerly, Professor at University of Rochester and at Columbia University.
Scott E. Royer, CFA, MBA	**Chief Financial Officer**. Formerly, Chief Financial Officer and Director of Finance of the Medical Films Group of Carestream Health, a medical and dental imaging company and an independent subsidiary of Onex Corporation, a Canadian publicly traded private equity investment firm. Mr. Royer earned an Executive MBA from Villanova University, and is a credentialed Chartered Financial Analyst (CFA)
Elizabeth E. Evans, Ph.D.	**Chief Operating Officer and Senior Vice President, Discovery and Translational Medicine**. Dr. Evans received an M.S. in Immunology and a Ph.D. in Pathology from the University of Rochester. Dr. Evans has held several leadership roles at Vaccinex since 2001 and holds several patents on SEMA4D/pepinemab.
Ernest S. Smith, Ph.D.	**Chief Scientific Officer and Senior Vice President, Research**. Dr. Smith received a Ph.D. in Immunology from the University of Rochester. Dr. Smith has held several leadership roles at Vaccinex since 2001 and holds several patents, including ActivMab® technology and Semaphorin 4D/pepinemab.
John E. Leonard, Ph.D.	**Senior Vice President, Development**. Formerly Vice President, Program Executive of Biogen Idec, Inc., a publicly traded biotechnology company. Dr. Leonard received a Ph.D. in Biochemistry from the University of California, Riverside

Vaccinex Scientific Advisors - Neurology

Eric Siemers, MD	President of Siemers Integration LLC. Distinguished medical fellow for Eli Lilly and Company's Alzheimer's Disease Global Development Team, founded and headed the Indiana University Movement Disorder Clinic. Served on the Board of Directors of the American Society of Experimental Neurotherapeutics, as founding member and Chair of the Alzheimer's Association Research Roundtable, and Steering Committee member for the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Karl D. Kieburtz, MD, MPH	President of Clintrex LLC, providing services regarding research and regulatory strategy for therapeutic development of interventions for brain disorders. Chair of the FDA Peripheral and Central Nervous System Drugs Advisory Committee and sits on the American Academy of Neurology (AAN) Clinical Research Subcommittee, the International Executive Committee of the Movement Disorders Society (MDS), the Board of Directors for the American Society for Experimental Neuro Therapeutics(ASENT), and the Council of the American Neurological Association (ANA),chair of the FDA Peripheral and Central Nervous System Drugs Advisory Committee.
Ira Shoulson, MD	Dr. Shoulson is a long time leader in Huntington's disease research. From 2011 to July 2018, Dr Shoulson was Professor of Neurology, Pharmacology and Human Science and Director of the Program for Regulatory Science and Medicine (PRSM) at Georgetown University where he was principal investigator of the FDA-Georgetown University Collaborating Center of Excellence in Regulatory Science and Innovation. From 1990 to 2011, Dr Shoulson was the Louis C. Lasagna Professor of Experimental Therapeutics and Professor of Neurology, Pharmacology and Medicine at the University of Rochester School of Medicine & Dentistry in Rochester, New York. Dr. Shoulson is an elected member of the National Academy of Medicine of the National Academy of Sciences.
Ralf Reilmann, MD	Founding Director and C.E.O. of the George-Huntington-Institute, Dept. of Radiology at the University of Muenster and the Dept. of Neurodegeneration and Hertie Institute for Clinical Brain Research at the University of Tuebingen.

Vaccinex Scientific Advisors - HNSCC Clinical Advisory Board

Barbara Burtness, MD	Professor of Medicine (Medical Oncology) at Yale, leader of the Disease Aligned Research Team for the Head and Neck Cancers Program and Co-Leader of the Developmental Therapeutics Research Program at Yale Cancer Center. Chair of ECOG-ACRIN Head and Neck Therapeutics Committee, served on the NCCN and SITC Head and Neck Guidelines Committee, and the NCI Head and Neck Cancer Steering Committee. Co-chair of the NCI Clinical Trials Planning Meeting on TP53-Mutated Head and Neck Cancer and FDA Project 2025 for Head and Neck. Founding Director of the Yale Head and Neck Cancer SPORE and has led numerous clinical trials, including the international phase III trial which led to regulatory approval of immunotherapy in first-line treatment of head and neck cancer.
Robert Haddad, MD	Chief, Division of Head and Neck Oncology. McGraw Chair, Head and Neck Oncology, Dana-Farber Cancer Institute. Professor, Medicine, Harvard Medical School.
Douglas Adkins, MD	Professor, Department of Medicine, Oncology Division, Medical Oncology, Washington University School of Medicine in St. Louis. NCI Head and Neck Steering Committee and Metastatic and Recurrent Head & Neck Cancer Task Force
Nabil Saba, MD	Director of the Head and Neck Cancer Medical Oncology Program at Winship Cancer Institute of Emory University, Professor and Vice Chair for Quality and Safety in the Department of Hematology and Medical Oncology and holds a joint appointment as Professor in the Department of Otolaryngology at Emory University School of Medicine. Chair of the National Cancer Institute's task force for recurrent metastatic head and neck cancer and Chair of the Rare Tumors Task Force of the National Cancer Institute's Head and Neck Cancer Steering Committee. Member of the NRG Oncology and Eastern Cooperative Oncology Group (ECOG) Head and Neck Cancer Core Committees, the ASCO clinical guidelines committee, and the ASCO Head and Neck Guideline Advisory Group.

Vaccinex Board of Directors

Albert D. Friedberg	Chairman, President and CEO of Friedberg Mercantile Group, a Toronto-based commodities and investment management firm he founded in 1971. He served as Chairman of the Toronto Futures Exchange from March 1985 to June 1988.
Chrystyna M. Bedrij	Co-Founder and Principal, Griffin Securities
Jacob B. Frieberg	Principal, The WTF Group.
Bala S. Manian, Ph.D.	Founder (or co-founder) of Quantum Dot Corporation, SurroMed, Biometric Imaging, LumisysInc., Molecular Dynamics and ReaMetrix.
Gerald E. Van Strydonck	Formerly, Managing Partner at PricewaterhouseCoopers.
Barbara Yanni	Formerly, Vice President and Chief Licensing Officer at Merck & Co., Inc.
Maurice Zauderer, Ph.D.	Vaccinex Founder, President and Chief Executive Officer. Formerly, Professor at University of Rochester and at Columbia University.