MULTIDISCIPLINARY HEAD and NECK CANCERS SYMPOSIUM

EXTRAORDINARY CARE: Collaborative, Targeted, Diverse, Patient Centered

JW Marriott Phoenix Desert Ridge Resort and Spa
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Phase 1/2 study of pepinemab in combination with pembrolizumab as first-line treatment of recurrent or metastatic head and neck cancer (KEYNOTE-B84)

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VACCINEX Science in the Service of Medicine

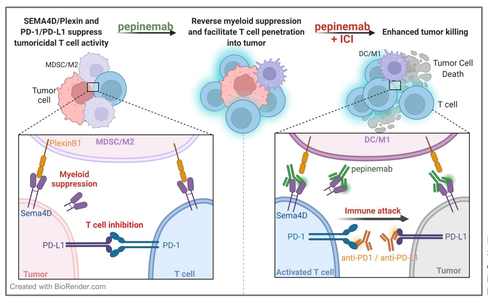
PURPOSE / OBJECTIVES

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) promotes tumor infiltration and activation of DCs and CD8+ T cells and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of ICIs. Pepinemab, a humanized SEMA4D blocking antibody, in combination with avelumab provided clinical benefit in some patients with difficult to treat ICI-resistant and PD-L1-low NSCLC. Pembrolizumab is approved as monotherapy or in combination with chemotherapy for the first-line treatment of recurrent or metastatic (R/M) HNSCC. More effective treatments are, however, needed to increase the frequency and duration of responses. The primary hypothesis of this proof-of-concept study is that pepinemab in combination with pembrolizumab will yield increased clinical benefit compared to the reported activity for pembrolizumab monotherapy in R/M HNSCC.

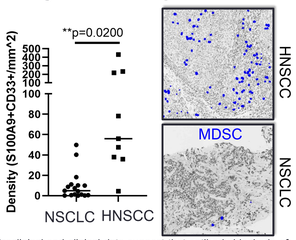
BACKGROUND

- Immunosuppressive myeloid cells in the TME are a critical resistance factor to the efficacy of ICIs in HNSCC.
- SEMA4D promotes recruitment and activity of immunosuppressive myeloid cells, including MDSC. (1, 2)
- Antibody blockade of SEMA4D enhances immune infiltration and reduces expansion and activation of MDSC.

Pepinemab's Unique MOA



High MDSC density in HNSCC

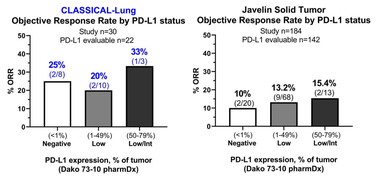


Preclinical and clinical data suggest that antibody blockade of SEMA4D promotes tumor infiltration and activation of dendritic cells and CD8+ T cell, and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of ICIs (1, 2).

CLINICAL PROOF OF CONCEPT

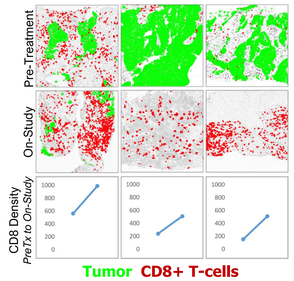
CLASSICAL-Lung Study

ORR in PD-L1 low/negative NSCLC



In a study evaluating pepinemab in combination with avelumab in patients with non-small cell lung cancer (NSCLC), treatment was well tolerated and demonstrated antitumor activity in patients with challenging ICI-resistant and PD-L1-low tumors. Biomarker analysis of biopsies demonstrated increased CD8 T-cell density correlating with RECIST response criteria (3).

Increased Penetration of Cytotoxic T-cells Following Treatment (pepinemab + avelumab)



PHASE 1b Case Studies

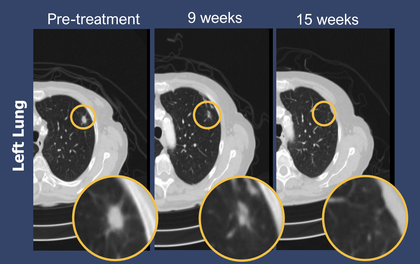
2 of 3 Complete Responses

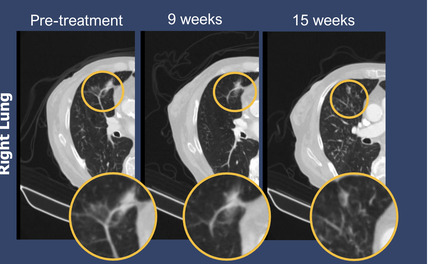
- **Recommended Phase 2 Dose (RP2D) determined:** Pepinemab (20mg/kg) and pembrolizumab (200mg), Q3W
- **No Dose Limiting Toxicities (DLT) observed**
- **Among first 3 patients enrolled in Phase 1b segment, two experienced complete response (CR), as per RECIST1.1**

Tumors in both responders expressed **low levels of PD-L1 biomarker (CPS<20)**, which have historically low response rates to PD-1/L1 antibodies administered as single agents.(4)

	Biopsy	Scans			Biomarkers	Adverse Events
Case Study # 1: CR (confirmed)	*week 5*	week 9	week 15	week 21		
Oropharyngeal cancer *Target lesions: metastatic lung lesions (Left 11mm, Right 15mm)*	NO malignancy	19% decrease, SD	100% decrease, CR	Confirmed, CR	PD-L1 **CPS<20** HPV **negative**	*none of notable severity*
Case Study # 2: CR (confirmed)						
Larynx cancer with direct invasion into thyroid and neck *Target lesions: neck mass (37mm)*	NO malignancy	100% decrease, CR	Confirmed, CR	Scan Pending	PD-L1 **CPS<1** HPV **negative**	*Grade 1 rash*
Case Study # 3: Non-evaluable						
Cancer of the tongue *Investigator Review: clinical progression withdrew from study at Week 6*	Tumor Present	Non-evaluable			PD-L1 **CPS<20** HPV **positive**	Unrelated to treatment (SAE) attributed to a pre-existing co-morbidity

Case Study # 1 Scans: Complete Response (confirmed)





TRIAL DESIGN: KEYNOTE-B84

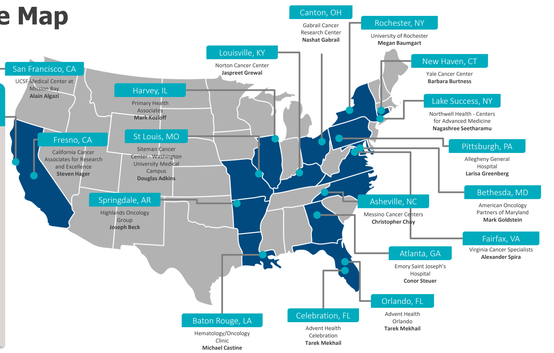
PHASE 1b	PHASE 2	OBJECTIVES
Safety Run-in **COMPLETE** n=3	Expansion Phase **ACTIVE ENROLLMENT** n=62	
20mg/kg pepinemab + 200mg pembrolizumab PD-L1 CPS All	RP2D: 20mg/kg pepinemab + 200mg pembrolizumab *(open label)* PD-L1 CPS *<20 n=31* *≥20 n=31*	Primary Efficacy Objectives ***ORR*** Exploratory Objectives ***PFS, DOR PK/PD Biomarkers of immune response***

Inclusion Criteria:
R/M HNSCC with measurable disease per RECIST1.1 (oropharynx, oral cavity, hypopharynx and larynx, and ECOG PS of 0 or 1)
Subjects who have received prior ICIs are excluded.

CURRENT ENROLLMENT

KEYNOTE-B84 Site Map

Total of 18 sites planned



PATIENT ACCRUAL*

Dr. J. Beck	2
Dr. C. Steuer	1
Dr. S. Hager	1
Dr. M. Baumgart	1
Dr. T. Mekhail	1
Dr. N. Seetharamu	1
Dr. D. Adkins	2

** As of February 22, 2022*

SUMMARY / CONCLUSION

- A major goal of current head and neck cancer research, and this study, is to identify a combination therapy that can increase the relatively small percentage of patients who benefit from current immuno- and other therapies.
- Phase 1b segment in 3 patients is complete. No DLTs were observed and treatment with pepinemab in combination with pembrolizumab was well-tolerated in KEYNOTE-B84.
- Early evidence of CRs was observed in two patients.
- The KEYNOTE-B84 study is accruing patients in the Phase 2 expansion phase, which plans to enroll up to an additional 62 patients in approximately equal groups of patients with CPS <20 and CPS ≥20 across 18 U.S. trial sites.

We would like to acknowledge Dr. Barbara Burtness (Yale Cancer Center), Dr. Douglas Adkins (Washington University), Dr. Nabil Saba (Winship Cancer Institute of Emory University), and Dr. Robert Haddad (Dana Farber Cancer Institute) for their thoughtful advice and contributions to our Clinical Advisory Board.

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1. Clavijo PE et al. Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function. Cancer Immunol Res. 2019 (2):282-291.
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This study was approved by WIRB Copernicus Group's Ethics Board on 11Feb2021; approval number 20210250.

Vaccinex is sponsoring the study and is conducted in collaboration with Merck Sharp & Dohme Corp, a subsidiary of Merck and Co, Inc.

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