KEYNOTE-B84

R/M HNSCC

Phase 1/2 study of pepinemab, an inhibitor of semaphorin 4D, in combination with pembrolizumab as first-line treatment of recurrent or metastatic head and neck cancer

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VACCINEX

#CT111

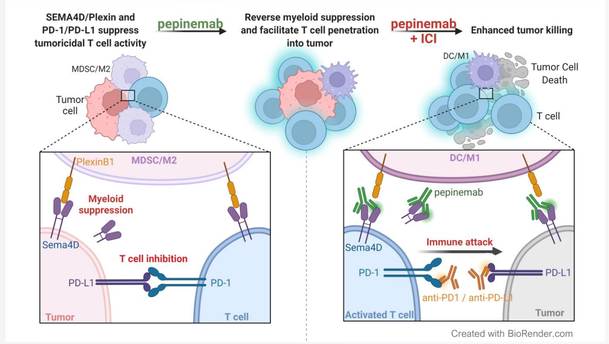
Abstract

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

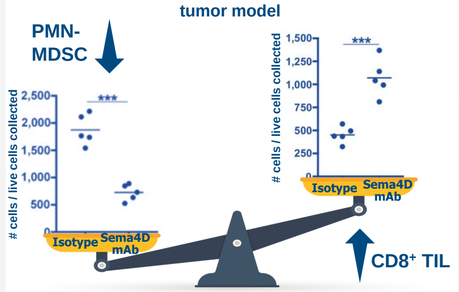
pepinemab's unique MOA

- Immunosuppressive **myeloid cells** in the TME represent an important **immune resistance** mechanism in **HNSCC**
- **SEMA4D** promotes **recruitment** and **activity** of immunosuppressive **myeloid cells**, including MDSC[2]
- Antibody **blockade** of SEMA4D **reduces recruitment** and **suppressive activity** of MDSC[1]
- Antibody **blockade** of SEMA4D **promotes tumor infiltration** and activation of DCs and CD8+ T cells[1,2]



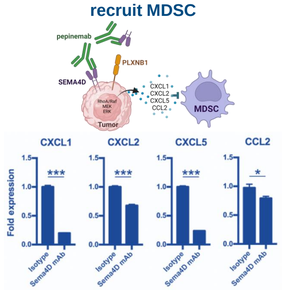
Preclinical proof of concept

SEMA4D antibody blockade shifts the balance of MDSC and T cells within TME of HNSCC MOC1 tumor model



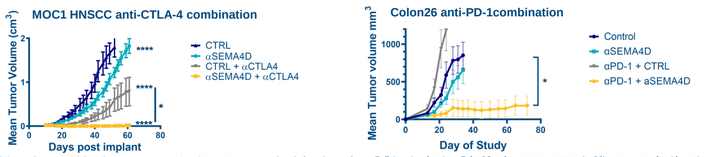
In vivo treatment with SEMA4D antibody reduces MDSC and increases CD8+ T cells in TME. Mice bearing MOC1 tumors were treated in vivo with Sema4D mAb or isotype control (0.2 mg weekly, n=5/group), tumors were dissociated and PMN-MDSC and CD8+ T cells were analyzed by flow cytometry [1].

SEMA4D blockade reduces secretion of chemokines that recruit MDSC



SEMA4D Mab blocks tumoral secretion of chemokines that recruit MDSC and TAM. MOC1 HNSCC cells in vitro were exposed to Sema4D mAb or isotype for 24 hours and analyzed for myeloid chemokine expression by qRT-PCR[1].

Immunomodulatory effects of SEMA4D blockade can enhance immune checkpoint therapies



C57Bl/6 mice bearing MOC1 subcutaneous tumors (n=10/group) were treated with four doses of 0.2 mg αSEMA4D or control antibodies weekly starting at day 4 after tumor implantation, and/or with three doses of 0.1 mg anti-CTLA-4 MAb (clone 9H10) every five days starting at day 10 after tumor implantation.

Balb/c mice bearing Colon26 subcutaneous tumors (n=20) were treated with anti-SEMA4D/MAb67 (10 mg/kg, weekly X2, starting on day2) and/or anti-PD-1/MAb RMP1-14 (10 mg/kg IP, twice weekly X4, starting on day 9 when tumor is palpable)

Trial Design

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.

Phase 1b Safety
3 patients
pepinemab + pembrolizumab *(open label)*
PD-L1 **CPS < and ≥ 20 (All)**
Complete

Phase 2 Expansion
up to 31 patients
pepinemab + pembrolizumab *(open label)*
PD-L1 **CPS < 20**
Active enrollment

up to 31 patients
pepinemab + pembrolizumab *(open label)*
PD-L1 **CPS ≥ 20**
Active enrollment

Objectives
Primary efficacy objective
ORR
Exploratory objectives
PFS, DOR
PK/PD
Biomarkers of immune response

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

KEYNOTE-B84 Phase 1b
Completed

DSMB approved advancing to expansion phase
Recommended Phase 2 dose (RP2D) determined:
pepinemab (20mg/kg) and pembrolizumab (200mg), Q3W

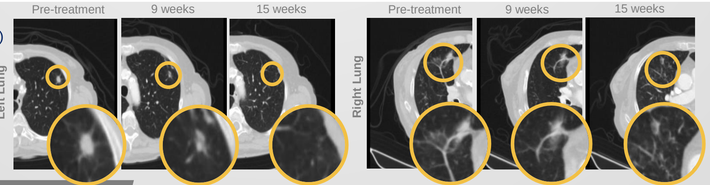
No dose limiting toxicities (DLT) observed
1 - grade 1 rash
1 - discontinued with non-treatment related SAE attributed to pre-existing co-morbidity

Observations
ORR – 2 confirmed CR among first 3 patients, as per **RECIST1.1**
Biomarker analysis
PD-L1, HPV status
Immune cell composition (pending)

Case Studies

	Biopsy Week 5	Scans Week 9	Week 15	→ Q6W	Biomarkers	Adverse events
Case Study # 1: CR (confirmed) *Oropharyngeal cancer* *Target lesions: metastatic lung lesions (Left 11mm, Right 15mm)*	No malignancy	19% decrease SD ↓19%	100% decrease CR	Confirmed CR (up to 27 wks)	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)



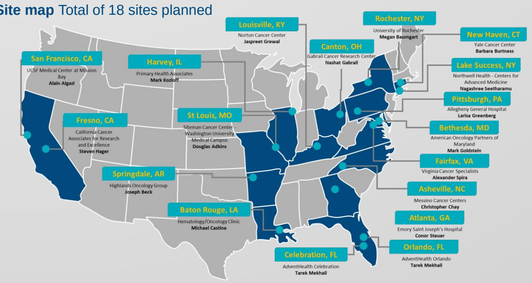
Current Enrollment

PATIENT ACCRUAL*

Dr. D. Adkins	3
Dr. J. Beck	2
Dr. C. Steuer	2
Dr. M. Baumgart	2
Dr. S. Hager	1
Dr. T. Mekhail	1
Dr. N. Seetharamu	1

*As of March 10th, 2022

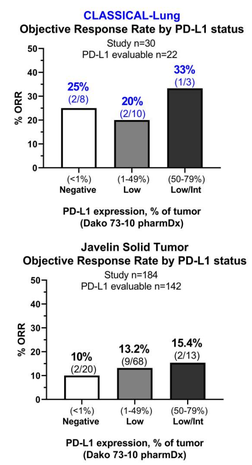
Site map Total of 18 sites planned



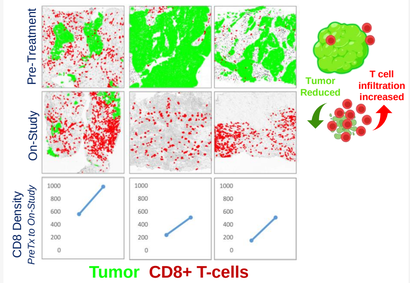
Clinical proof of concept

CLASSICAL-Lung study[3]

A. Higher response rate in difficult to treat PD-L1-low NSCLC with combination therapy



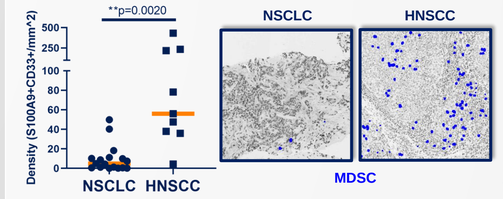
B. Increased penetration of cytotoxic T-cells following treatment (pepinemab + avelumab)



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.
A. Note that a score of 80% in Merck KGaA 73-10 assay employed here is equivalent to a score of 50% in The 22C3 assay employed by US Merck.
B. Biomarker analysis of biopsies demonstrated increased CD8 T-cell density correlating with RECIST response criteria.

Rationale for trial in HNSCC

High MDSC density in HNSCC



MDSC densities were assessed in patient biopsies. Pre-treatment biopsies from patients with advanced non-small lung cancer (NSCLC, n=17) and resectable head and neck cancer (n=9) were analyzed for presence of MDSC.

Head and neck cancer (HNSCC)

- Preclinical data suggest that SEMA4D is strongly expressed in HNSCC & induces high levels of myeloid derived suppressor cells (MDSC)[1]
- Relatively low (17-19%) response rate to immune checkpoint therapy in HNSCC[4]
- Preclinical and clinical data suggest that antibody blockade of SEMA4D reverses immunosuppression, including attenuation of MDSC recruitment and function[1, 2]
- ***Hypothesis:*** Inhibiting MDSC with pepinemab may enhance response to pembrolizumab in tumors with high myeloid suppression, including HNSCC

Summary

GOAL
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 SAFETY
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.

OBSERVATIONS
2 confirmed **Complete Responses** were observed in first 3 patients.
CR's were both **PD-L1 low** and **HPV negative.**

PHASE 2
The **KEYNOTE-B84** study is **actively enrolling 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. Douglas Adkins (Washington University), Dr. Barbara Burtness (Yale Cancer Center), 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.

References:
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.

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