VACCINEX
#434

Phase 1/2 study to evaluate pepinemab in combination with pembrolizumab in advanced, recurrent or metastatic head and neck cancer (KEYNOTE B84)

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OBJECTIVE

The purpose of the study is to evaluate the safety, tolerability, and efficacy of pepinemab in combination with pembrolizumab and determine a recommended Phase 2 dose (RP2D) in patients with advanced, recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). The study will consist of a safety run in phase and a dose expansion phase.

The primary hypothesis is that the combination of pepinemab + pembrolizumab is superior to SOC pembrolizumab with respect to ORR. Pepinemab's proposed mechanism of action to facilitate infiltration of cytotoxic CD8+ T cells and reduce inhibitory and suppressive cells, such as myeloid derived suppressor cells (MDSC).

BACKGROUND

❖ Immunosuppressive myeloid cells in the tumor microenvironment (TME) are a critical resistance factor to the efficacy of immune checkpoint inhibitors (ICIs) in patients with head and neck squamous cell carcinoma (HNSCC).

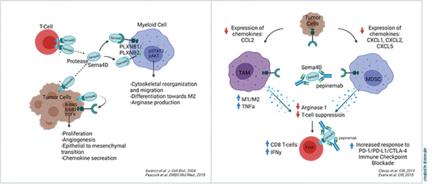
❖ Both semaphorin 4D (SEMA4D, CD100) and MDSCs are reported to play important roles in the growth and progression of HNSCC.

❖ Preclinical and clinical data demonstrated 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, 3).

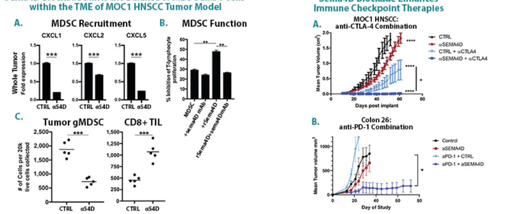
❖ In a study evaluating pepinemab, a humanized SEMA4D blocking antibody, in combination with avelumab in patients with non-small cell lung cancer, the combination appeared to provide clinical benefit in patients with difficult to treat ICI-resistant and PD-L1-low tumors (4).

❖ Pembrolizumab is approved as first line therapy as monotherapy or in combination with chemotherapy in recurrent or metastatic (R/M) HNSCC, however not all patients respond to ICIs. More effective treatments are required.

Semaphorin4D-Plexin Signaling Drives Immune Exclusion and Suppression of T-cell Response in Solid Tumors



Preclinical Proof of Concept



SEMA4D antibody blockade shifts the balance of MDSC and T cells within TME of HNSCC model. A) SEMA4D antibody reduces tumoral expression of chemokines that recruit MDSC. MOC1 HNSCC cells in vitro were exposed to Sema4D mAb (10 µg/mL) or isotype for 24 hours and analyzed for myeloid chemokine expression by qRT-PCR (in vitro tumor). **B) SEMA4D induces MDSC suppression of T cell proliferation, SEMA4D antibody reverses this effect.** MDSC were isolated from HNSCC MOC1 in vivo tumors and co-cultured ex vivo with rSEMA4D (10 µg/ml) or antibodies, in presence of naïve T cells labeled with CFSE in a T cell suppression assay. **C) 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 subjected to a percoll gradient, gMDSC and CD8+ T cells were analyzed by flow cytometry (1).

Immunomodulatory effects of SEMA4D blockade can enhance immune checkpoint therapies. Two preclinical models: **A**) MOC1 HNSCC (5x106 cells) were subcutaneously implanted into C57Bl/6 mice, then treated with α SEMA4D/MAb67 (10 mg/kg, weekly IP), αCTLA-4 / MAb 9H-10 (5 mg/kg, q5D); n=10 (1). **B**) Colon26 (500,000 cells) were subcutaneously implanted into Balb/c mice, and treated with αSEMA4D / MAb67 (10 mg/kg, weekly IP X4), αPD-1 / MAb RMP1-14 (10 mg/kg, twice/week, starting on day10, n=20).

TRIAL DESIGN

Although pembro and pembro / chemo is approved for R/M HNSCC, rational combinations are still needed because most patients (70-80%) do not respond, many of the responses are short-lived, and many patients cannot tolerate chemotherapy. Pepinemab's unique mechanism of action paired with its low toxicity complements immune checkpoint therapy well. Pepinemab facilitates T-cell infiltration and reduces immune suppression while immune checkpoint inhibitors sustain T-cell activity. Combination therapy has the potential to overcome multiple immune resistance mechanisms filling an unmet need.

KEYNOTE B84 (NCT04815720) is a multicenter, single-arm open-label study to evaluate the safety, efficacy, PK/PD of pepinemab in combination with pembrolizumab in subjects with locally advanced, R/M HNSCC.
This study is conducted in collaboration with
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

CONDITIONS
Metastatic Squamous Cell Carcinoma of the Head and Neck (HNSCC)

DRUG
pepinemab + pembrolizumab
(open label)

PHASE
Phase 1 - Safety Run-in
Phase 2 - Dose Expansion

PARTICIPANTS
n=80
≥18 Years old
All Genders
Does not accept healthy volunteers

DATES
Start Date
August 9, 2021
Estimated Completion Date
September 4, 2023

Sponsor: VACCINEX

De-escalation of pepinemab
**(only if required as defined in protocol)*
15 or 10 mg/kg pepinemab
+
200 mg pembrolizumab

PHASE 1b Safety Run-in
20 mg/kg pepinemab
+
200 mg pembrolizumab
n=3-6

PD-L1 combined positive score
All

PHASE 2 Dose Expansion Phase
20 mg/kg pepinemab
+
200 mg pembrolizumab
(20mg/kg pepinemab expected dose - may change based on safety run-in phase)

n=62

PD-L1 combined positive score
<20 (n=~31)
≥20 (n=~31)

Primary Efficacy Objectives
ORR
Exploratory Objectives
PFS, DOR
PK/PD
Biomarkers of immune response

Subjects with measurable disease per RECIST1.1 will be enrolled, including oropharynx, oral cavity, hypopharynx and larynx, and ECOG PS of 0 or 1. Subjects who have received prior ICIs are excluded.

Subjects will undergo evaluation for extent of disease (EOD) at baseline, week 9, every 6 weeks through year 1, and every 9 weeks thereafter. Subjects who discontinue study treatment will continue to be followed for survival every 12 weeks after safety follow-up (for up to approximately 2 years).

OBJECTIVES

Primary Objective

The Dose Expansion phase of the study is to evaluate objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 of the combination of pepinemab/pembrolizumab in immunotherapy naïve patients with advanced R/M HNSCC.

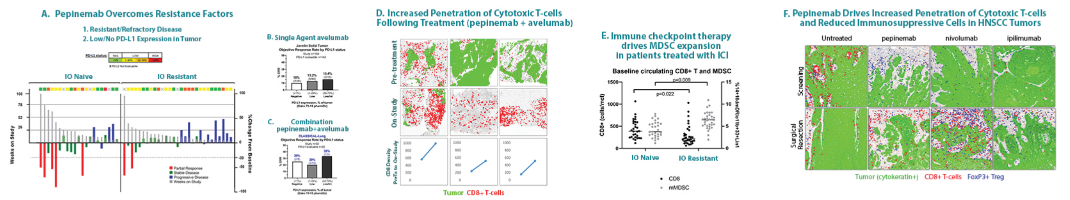
Secondary Objectives

- Evaluate progression-free survival (PFS) by RECIST 1.1 of the combination of pepinemab/pembrolizumab in immunotherapy naïve patients with advanced R/M HNSCC
- Evaluate the overall survival (OS)
- Evaluate duration of response (DOR).

Exploratory Objective

- Evaluate PFS, ORR, and DOR via the iRECIST criteria.
- Evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of the combination.
- Investigate the relationship between treatment with pepinemab and pembrolizumab and certain biomarkers and the genomic signatures of baseline or archival tumor samples.

Immune Checkpoint Combinations in the Clinic



Immunomodulatory effects of SEMA4D blockade can enhance immune checkpoint therapies and promote T cell infiltration. CLASSICAL-Lung study investigated combination treatment of pepinemab and avelumab in patients with NSCLC. Pepinemab has shown to be well tolerated and does not enhance immune-related toxicities of partner drug. **A**) Combination therapy overcomes unmet need, demonstrating anti-tumor activity in PD-L1 low or PD-L1 negative tumors. **B**) The reported single agent avelumab ORR is ~10-15% in PD-L1 low/negative tumors (Javelin Solid Tumor)(4). **C**) A 2-3x increase in ORR was observed with combination therapy of pepinemab plus avelumab (25-33%). **D**) Combination therapy increased the CD8+ T cell density and correlated with antitumor activity in tumors that were resistant/refractory to prior therapy with single-agent checkpoint inhibitors. **E**) Circulating CD8s are lower and MDSC higher at baseline in IO resistant subjects. Accumulation of myeloid suppressors drives resistance/refractory tumors (4).

F) Biomarker analysis of immunophenotype in HNSCC tumors. Patients enrolled in integrated biomarker study at Emory University (NCT03690986) received one treatment with pepinemab, nivolumab, or ipilimumab before surgical resection of tumor. Treatment-induced changes in immunophenotype for each patient screening biopsy (top) and surgical resection (bottom) are shown. CD8+ T cells (red), Treg (blue) overlays on cytokeratin stain (green) at tumor invasive margin are shown.

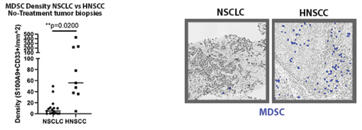
Pepinemab's Unique MOA Addresses an Unmet Need in HNSCC

❖ MDSC represent an important mechanism of resistance to ICI

❖ HNSCC have relatively high levels of MDSC

❖ SEMA4D is abundantly expressed in HNSCC and drives MDSC accumulation and resistance to ICI (1,2,5)

❖ Pepinemab treatment is a rational combination therapy with ICI in HNSCC due to unique MOA
 ↑ Increase T cell Infiltration
 ↓ Reduce Immunosuppression



MDSC levels were assessed in patient biopsies. Pre-treatment biopsies from the CLASSICAL-Lung (NSCLC) trial were analyzed along with pre-treatment and no treatment biopsies from integrated biomarker trial (NCT03690986) for HNSCC.

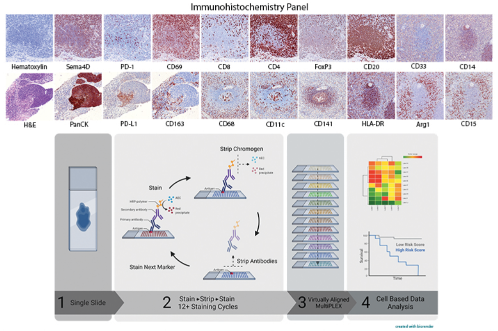
UPDATE

Enrollment and screening of patients has been initiated. A total of 18 clinical sites in US are planned.

Site Status	Site Name	City/State	Principle Investigator
Recruiting	California Cancer Associates for Research and Excellence	Fresno, California	S. Hager
Recruiting	AdventHealth Orlando	Orlando, Florida	T. Mekhail
Recruiting	AdventHealth Celebration	Celebration, Florida	G. Simon
Setup	UCSF Medical Center at Mission Bay	San Francisco, California	A. Algazi
Recruiting	Gabrail Cancer Research Center	Canton, Ohio	N. Gabrail
Recruiting	Siteman Cancer Center - Washington University Medical Campus	Saint Louis, Missouri	D. Adkins
Recruiting	Emory Saint Joseph's Hospital	Atlanta, Georgia	C. Steuer
Setup	Northwell Health - Centers for Advanced Medicine	Lake Success, New York	N. Seetharamu
Recruiting	University of Rochester	Rochester, New York	M. Baumgart
Setup	Allegheny General Hospital	Pittsburgh, Pennsylvania	L. Greenberg
Recruiting	American Oncology Partners of Maryland, PA	Bethesda, Maryland	M. Goldstein
Recruiting	Virginia Cancer Specialists - Fairfax	Fairfax, Virginia	A. Spira
Setup	Norton Cancer Center	Louisville, Kentucky	J. Grewal
Setup	Yale Cancer Center	New Haven, Connecticut	B. Burtness
Recruiting	Primary Health Associates - Primary Health Oncology - Harvey (Monroe Medical	Harvey, Illinois	M. Kozloff
Recruiting	Highlands Oncology Group, PA - North Hills	Springdale, Arkansas	J. Beck
Recruiting	Messino Cancer Centers (MCC) - Asheville	Asheville, North Carolina	C. Chay
Recruiting	Hematology/Oncology Clinic-Baton Rouge	Baton Rouge, Louisiana	M. Castine
Setup	Univeristy of Texas Health Science Center at San Antonio	San Antonio, Texas	J. Sarantopoulos

Planned Biomarker Analysis

Immunohistochemistry Panel



CONCLUSIONS

There remains a clear unmet need for more effective immunomodulatory treatment options to overcome immunosuppressive factors in the TME. The KEYNOTE B84 study will evaluate the combination of pepinemab with pembrolizumab as a potential treatment option to overcome resistance to and enhance activity of pembrolizumab in HNSCC.

ACKNOWLEDGEMENTS / REFERENCES

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This study was approved by WIRB Copernicus Group's Ethics Board on 11Feb2021; approval number 20210250.

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