Pepinemab, anti semaphorin 4D antibody, in combination with pembrolizumab induced formation of organized lymphoid aggregates and enhanced response to treatment in CPS<20 R/M HNSCC tumors (KEYNOTE-B84)

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Abstract # 676

KEYNOTE-B84 TRIAL DESIGN: R/M HNSCC

KEYNOTE-B84

- R/M HNSCC, First-line, Immunotherapy naïve
- **Treatment**: 20mg/kg pepinemab + 200mg pembrolizumab, Q3W

Harmonize inclusion / exclusion criteria of KEYNOTE-048 Phase 3 study, reference for historical comparison of single agent KEYTRUDA

Phase 1b

Safety

Phase 2

Efficacy

Pre-specified Interim Analysis (36 patients)

Outcome Measures

Safety

Objective Response

Biomarker Outcomes

SUMMARY

SAFETY

Pepinemab plus pembrolizumab appears well-tolerated in HSNSCC patients, supporting the overall favorable safety profile of pepinemab in combination with ICI

EFFICACY

Pepinemab plus pembrolizumab appears to increase ORR and PFS compared to historical checkpoint monotherapy in R/M HNSCC with CPS <20

~2X

BIOMARKER

IHC data suggest that pepinemab combined with ICI induced TLS and stem-like CD8+ T cells to enhance tumor immunity & clinical benefit, especially in patients with hard-to-treat HPV-negative and CPS<20 disease

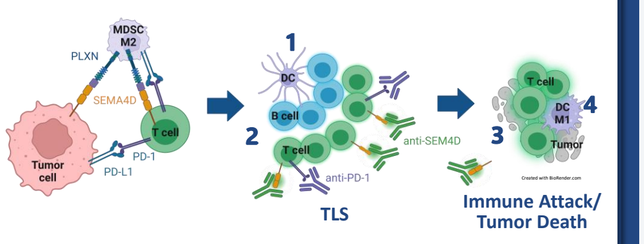
OVERALL CLINICAL POC

Data from KEYNOTE-B84 Interim Analysis supports unique mechanism of action and activity in PD-L1-low disease, consistent with prior completed studies: neoadjuvant melanoma NSCLC

BACKGROUND

Unfavorable balance of immunosuppressive myeloid cells over activated APC 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) reverses immunosuppression, including attenuation of MDSC recruitment and function[1] and promotes organization of lymphoid aggregates within tumors[2], leading to enhanced efficacy of ICIs. **Pepinemab, a SEMA4D blocking antibody**, in combination with anti-PD-L1 was well tolerated and provided clinical benefit in patients with ICI-resistant, PD-L1-low NSCLC[3]. ***The primary hypothesis of this proof-of-concept study is that pepinemab in combination with pembrolizumab will improve the efficacy of immunotherapy in R/M HNSCC.***

SEMA4D Immune Suppression | **Anti-SEMA4D Immune Enhancement**



- Ligand SEMA4D expressed on Tumor and Lymphocytes
- Receptor Plexin B1/B2 (PLXN) expressed on Myeloid cells
- Ligand:Receptor engagement induces recruitment / suppressive Myeloid function
- Inhibit T cell function

Pepinemab in combination with pembrolizumab

1) Activates Dendritic Cells
2) Induces Tertiary Lymphoid Structures (TLS)
3) Expands T cells in Tumor
4) Reverses Myeloid Immunosuppression

Well tolerated

Pepinemab does *not* appear to increase toxicities of partner drug.

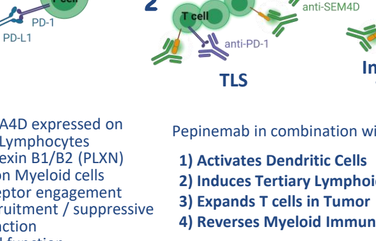
NSCLC	Melanoma	HNSCC
Combo with anti-PD-L1 NCT03268057	Combo with anti-PD-1 and/or anti-CTLA4 NCT03769155	Combo with anti-PD-1 or anti-CTLA4 NCT04815720

Unmet need

Pepinemab in combination with anti-PD-L1 → antitumor activity observed in immune checkpoint resistant/ refractory NSCLC, ***including PD-L1 low/negative tumors[3]***

PD-L1 Low	Combination of pepinemab with anti-PD-L1 **ORR ~ 25-33%**	Reported single agent anti-PD-L1: **ORR~10-15%**

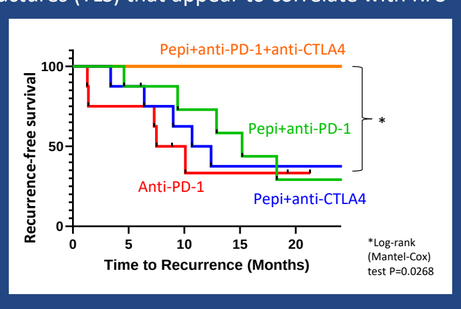
Pepinemab improves T cell infiltration and reverses myeloid suppression

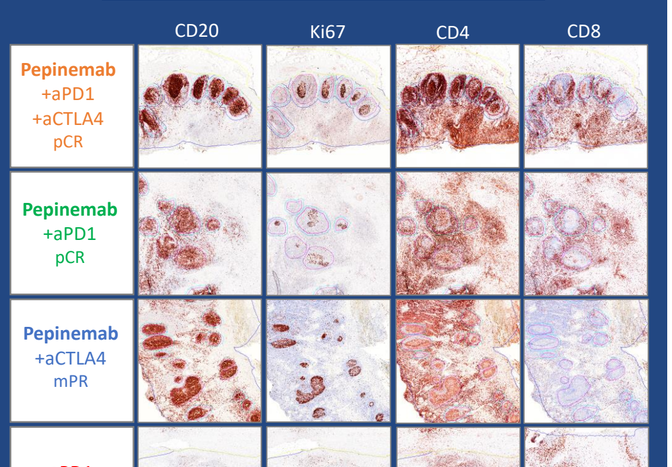


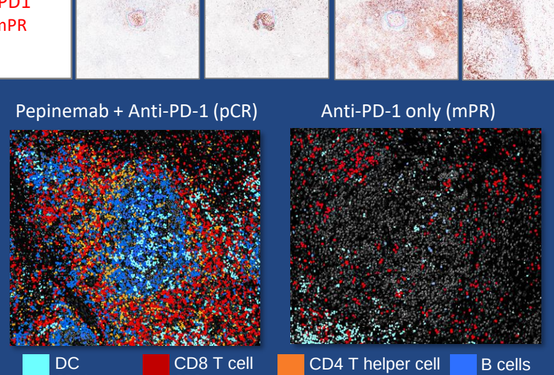
Neoadjuvant treatment with pepinemab in patients with metastatic MSS Colorectal Cancer, *in collaboration with Winship Cancer Institute, Emory University integrated biomarker study (NCT03373188)*[4]

Induction of Tertiary Lymphoid Structures (TLS)

Pepinemab increases organization of tertiary lymphoid structures (TLS) that appear to correlate with RFS







Melanoma patients received 2 doses of neoadjuvant immunotherapy (Day1&21) before surgery (day 35-49), n=8/group. Data from resected tumors is shown. pCR: pathologic complete response; mPR: major pathologic response. *Investigator sponsored trial NCT03690986, in collaboration with Emory University*

RESULTS: KEYNOTE-B84 Interim Analysis

Tumor Response

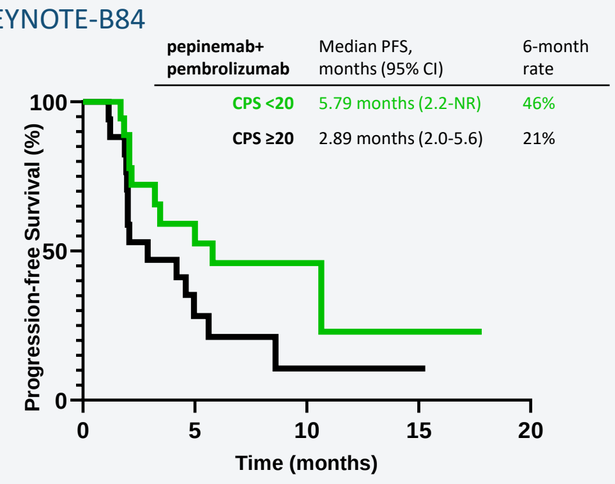
~ 2x increase in ORR, DCR, and PFS in CPS <20 with pepi+pembro combination treatment, compared to historical control[7]

	PD-L1 low						PD-L1 high	
	CPS <1			CPS 1-19		CPS <20	CPS ≥20	
	KN-B84 PEPI+Pembro		KN-048 Pembro	KN-B84 PEPI+Pembro	KN-048 Pembro	KN-B84 PEPI+Pembro	KN-048 Pembro	KN-B84 PEPI+Pembro	KN-048 Pembro
Total (n)	(7)		(44)	(12)	(124)	(19)	(168)	(17)	(133)
CR	(1)	**14.3%**	**0.0%**	(1) 8.3%	3.2%	(2) 10.5%	2.4%	(1) 5.9%	7.5%
PR	(0)	0%	4.5%	(2) 16.7%	11.3%	(2) 10.5%	9.5%	(2) 11.8%	15.8%
SD	(2)	28.6%	22.7%	(7) 58.3%	25.8%	(9) 47.4%	25.0%	(4) 23.5%	30.1%
ORR	(1)	**14.3%**	**4.5%**	(3) **25.0%**	**14.5%**	(4) **21.1 %**	**11.9%**	(3) 17.6%	23.3%
DCR	(3)	**42.9%**	**27.3%**	(10) **83.3%**	**40.3%**	(13) **68.4%**	**36.9%**	(7) 41.2%	53.4%
mPFS months (95% CI)						**5.79** (2.2 - NR)	**2.2** (2.1-2.9)	2.89 (2.0-5.6)	3.4 (3.2-3.8)

Progression-free Survival

KEYNOTE-B84

pepinemab+ pembrolizumab	Median PFS, months (95% CI)	6-month rate
CPS <20	5.79 months (2.2-NR)	46%
CPS ≥20	2.89 months (2.0-5.6)	21%



Safety

No concerning safety signals identified
In 3 successive SMC meetings PIs and medical monitor have unanimously **approved the study to move forward** with no modifications

AEs appear to be either **disease-related** or prior medical history related and are low grade (Grade 1-2)

PK/PD

Serum PK levels of pepinemab are **as expected** from previous trials

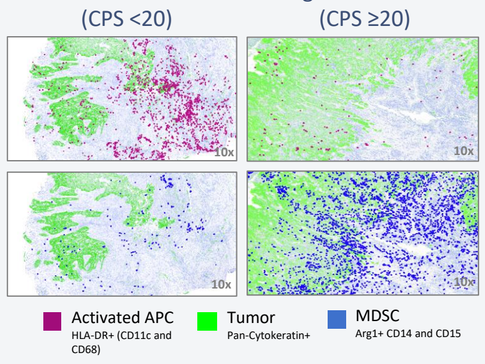
ALL subjects dosed to date show **complete saturation of SEMA4D** (receptor occupancy) after the first dose, and saturation is maintained throughout the dosing period

ADAs generated are **mainly low titer** (<50), do not influence pharmacodynamics

Biomarker : Multiplex IHC from Pre and On-Tx biopsies

Data suggest that treatment improved balance of activated APC and MDSC and induced the presence of highly organized immune aggregates consisting of high density of B cells, DC and T cell zones, and correlating with disease control.

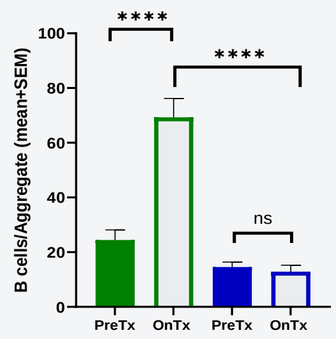
Reprogram myeloid cells: ↑ HLA+ APC ↓MDSC



On-treatment patient biopsies from patients with disease control show high density of activated HLA-DR+ APC (CD68+ and CD11c+) and low levels of suppressive Arg1+ MDSC (CD15+ and CD14+). In contrast, low HLA-DR+ APCs and higher levels of Arg1+ MDSC are observed with disease progression.

- **Treatment appears to reverse the immunosuppressive tumor microenvironment in patients who experienced clinical benefit, compared to those with progressive disease.**

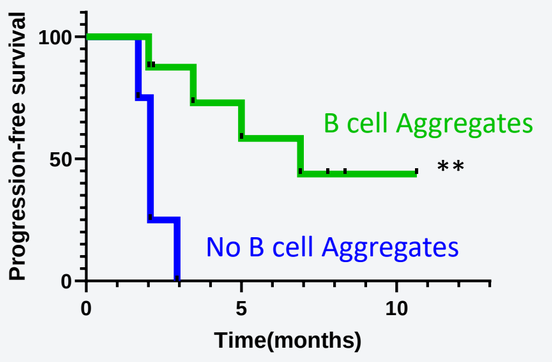
High Density B cell aggregates induced with Treatment



Patients who experience clinical benefit (Disease Control) during treatment with pepinemab and pembrolizumab have a higher frequency of mature immune aggregates with a high density of B cells in their on-treatment biopsy (n=7) compared to their pre-treatment biopsies (n=16), p<0.0001. This difference is not observed in on- (n=5) and pre-treatment biopsies (n=10) from patients with disease progression. One-way ANOVA, **** p<0.0001; ns = not significant, p≥0.05.

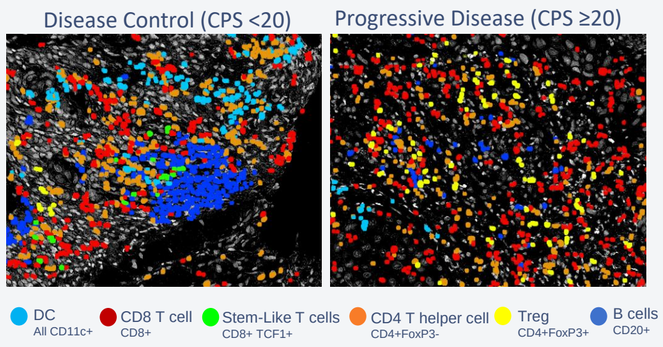
Immune Aggregates correlate with PFS

Longer progression free survival (PFS) with presence of B cell aggregates

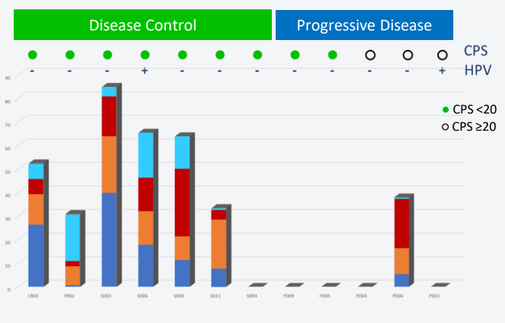


B cell aggregates correlate with PFS. On-treatment biopsies with one or more B cell aggregates positively correlates with longer progression-free survival. N=12 on-treatment biopsies at interim analysis. Log Rank survival statistical analysis resulted in a ** p value of 0.0056.

B cell aggregates are highly organized with key immune cells for antigen presentation and expansion of T cells

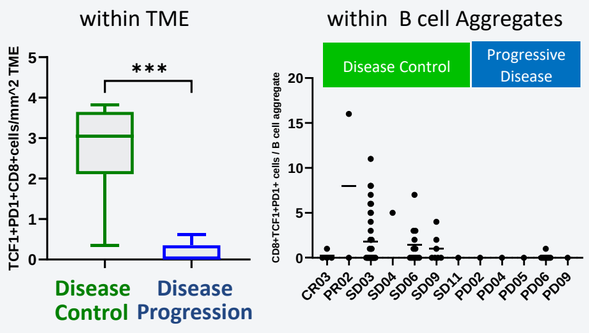


Treatment appears to induce durable disease control associated with an increase in number of TLS and proportion of DC's within TLS



Patients experiencing disease control following treatment with pepinemab plus pembrolizumab showed an increase in the number of B cell aggregates (above). **These aggregates exhibit spatial organization that is characteristic of functional immune response, similar to mature TLS.** Highly organized immune aggregates contain zones of high-density APCs (activated DC, B cells) and a T cell zone with CD8, CD4 T helper cells and stem-like CD8's. In contrast, patients with progressive disease and untreated patient tumors predominantly contain no or few immune aggregates with spatial interactions that favor immune suppression, including abundance of Treg.

TCF1+PD1+CD8+ Stem-like progenitor cells appear to be associated with Disease Control and located within B cell aggregates



Stem-like CD8 are associated with improved response to immunotherapy and share features with T_{FH} cells found within immune aggregates. Patients with disease control had a higher density of stem-like CD8 T cells after treatment within the TME. Stem-like CD8 T cells are located within B cell aggregates.
Statistical analysis: Two tailed unpaired t test, P<0.05

METHODS

- **Single-arm, open label, phase 1b/2 study**
- **18 medical centers in USA**
- **Inclusion**: pathologically confirmed R/M SCC; ECOG ≤ 1
- **Exclusion**: progressive disease within 6 months of curatively intended systemic treatment given for locoregionally advanced disease, symptomatic CNS metastases, active autoimmune disease

DEMOGRAPHICS

	KEYNOTE-B84 Pepi + Pembro N=36		KEYNOTE-048 Pembro N=301	
Age (median years)	66 (33-81)		62 (56-68)	
Sex				
Female	8	22%	51	17%
Male	28	78%	250	83%
Race				
Asian	3	8%	-	-
Black or African American	6	17%	-	-
Mexican	1	3%	-	-
White	25	69%	-	-
Unknown	1	3%	-	-
ECOG Performance Status Score				
0	11	31%	118	39%
1	25	69%	183	61%
Smoking Status				
Current or Former	20	56%	239	79%
Non-Smoker	16	44%	62	21%
HPVp16				
Positive	4	11%	63	21%
Negative	32	89%	238	79%
PD-L1 CPS				
≥20	17	47%	133	44%
1-19	12	33%	124	42%
<1	7	19%	44	15%
TPS				
≥50	13	36%	67	22%
<50	23	64%	234	78%
Primary Tumor Location				
Hypopharynx	1	3%	38	13%
Larynx	2	6%	74	25%
Oral Cavity (tongue, cheek, teeth)	13	36%	82	27%
Oropharynx	18	50%	113	38%
Pharynx	1	3%	-	-
Sinonasal	1	3%	-	-

IHC Biomarker Analysis

PD-L1 expression in archival or newly obtained FFPE tumor samples was assessed at a central lab using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and characterized by combined positive score (CPS)

HPV p16 status for oropharyngeal cancers was assessed at a central lab using the CINtec p16 Histology assay (Ventana Medical Systems, Tucson, AZ, USA)

MULTIPLEX IHC assessment of TME

(Biopsies collected pre-treatment screening and at week 5 cycle 3)

1. Stain → Image → Strip → Stain ~14 staining cycles per slide

Lymphocyte Panel	APC Panel	Myeloid Panel
Hematoxylin	Hematoxylin	Hematoxylin
Sema4D	Sema4D	CD33
PD-1	CD163	CD15
CD69	CD11c	CD14
CD8	HLA-DR	Arg1
CD4	CD68	HLA-DR
FoxP3	CD141	Sema4D
CD26	CD206	S100A9
CD20	Arg1	CD16
CD39	PanCK	PanCK
CD45	PD-L1	PD-L1
TCF1		
PanCK		
Ki67		

2. Virtually align stains by panel using Visiopharm Tissuealign

3. ROI drawn around **pathologist identified tumor area, includes tumor and tumor-associated stroma**

4. Image analysis software, Visiopharm algorithms were written and **automated** to identify cell phenotypes, quantify density within entire tumor area, neighborhoods.

5. **Unbiased Software algorithm identifies B cell aggregates** using heatmaps to determine B cells clustering within 50um of each other.

6. **B cell aggregates classified by**

Low Density B cells (<20 cells)

High Density (Mature) B cell aggregates [5,6] (≥20 cells)

7. Expand B cell hubs by 150um to **identify cells interacting with B cells and classify other cells within immune aggregates**

RECEPTOR OCCUPANCY ASSAY: Vaccinex flow-cytometry-based assay to determine antibody saturation of target SEMA4D in blood[8]

NEXT STEPS

Based on these findings, we and our pharmaceutical collaborator Merck Sharp & Dohme LLC (a subsidiary of Merck & Co., Inc., Rahway, NJ, USA), are in the preliminary testing and design stages of a potential extension of this study that may focus on treatment with pepinemab and pembrolizumab in combination with chemotherapy.

Ongoing Trials pepinemab combination therapies

- **PDAC (NCT05102721): Pepi+ICI** — University of Rochester, Merck KGaA
- **Neoadjuvant HNSCC (NCT03690986): Pepi+ICI** — Emory University, BMS
- **Breast Cancer (NCT05378464): Pepi + DC ACT** — H.Lee Moffit Cancer Center

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