Correlative and spatial biomarker analysis of a phase 1/2b study to evaluate **PEPINEMAB IN COMBINATION WITH PEMBROLIZUMAB** for first-line treatment of patients with recurrent or metastatic head and neck cancer

#2603

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Pepinemab in combination with Pembrolizumab

KEYNOTE-B84

- **Single-arm, open label, phase 1b/2 study**
- **Analysis stratified by PD-L1 status**
- **18 medical centers in USA**

Inclusion: pathologically confirmed R/M SCC; ECOG ≤ 1, immunotherapy naive
Exclusion: progressive disease within 6 months of curatively intended systemic treatment given for locoregionally advanced disease, symptomatic CNS metastases, active autoimmune disease.
Study design mimics KEYNOTE-048.

Treatment
20mg/kg pepinemab
+ 200mg pembrolizumab, Q3W

Phase 1b Safety

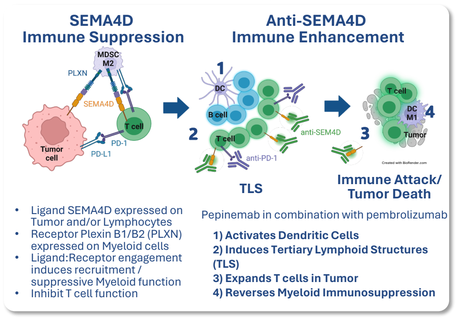
Phase 2 Efficacy
Pre-specified Interim Analysis
(36 patients)
Current Enrollment 49 patients

Outcome Measures
Safety
Objective Response
Biomarker Outcomes

KEYNOTE-B84 (NCT04815720) is an ongoing single-arm open-label study evaluating the safety, efficacy, and PK/PD of pepinemab in combination with pembrolizumab as first-line treatment of recurrent or metastatic HNSCC. Exploratory biomarker analyses were performed to evaluate spatial interactions of tumoral immune cells. Pre- and on-treatment tumor biopsies were collected and assessed by multiplex immunohistochemistry for up to 36 biomarkers/biopsy. Unbiased algorithms identified co-localization of markers for advanced cell phenotyping, density, spatial and proximity analysis. Biomarker results were then stratified by demographic and clinical outcome measures.

Background

Myeloid cells contribute to suppression of adaptive immunity within the TME and limit the efficacy of immune checkpoint inhibitors (ICIs) in head and neck squamous cell carcinoma (HNSCC). Semaphorin 4D (SEMA4D) signaling through its receptors (PlexinB1/B2,CD72) promotes recruitment and suppressive function of myeloid suppressor cells (MDSC).[1] Blocking antibody to SEMA4D attenuated MDSC and increased penetration and organization of dendritic cells (DC) and T cells into tertiary lymphoid structures that enhanced activity of ICI in preclinical and clinical studies.[1,2] **Pepinemab**, in combination with anti-PD-L1 was well tolerated and provided clinical benefit in patients with ICI-resistant, PD-L1-low NSCLC[3]. We hypothesize that SEMA4D blocking antibody pepinemab may regulate infiltration and crosstalk of immune cells in TME as a novel and complementary mechanism of immune enhancement when combined with immune checkpoint therapy.



- Ligand SEMA4D expressed on Tumor and/or 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

Tumor Response

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

	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	(6)		44	(13)		(124)	(19)		(168)	(17)		(133)
CR	1	16.7%	0.0%	1	7.6%	3.2%	2	10.5%	2.4%	1	5.9%	7.5%
PR	0	0%	4.5%	2	15.4%	11.3%	2	10.5%	9.5%	2	11.8%	15.8%
SD	2	33.3%	22.7%	8	61.5%	25.8%	10	52.6%	25.0%	5	29.4%	30.1%
ORR	1	**16.7%**	4.5%	**3**	**23.1%**	14.5%	4	**21.1 %**	11.9%	3	17.6%	23.3%
DCR	**3**	**50.0%**	27.3%	**11**	**84.6%**	40.3%	**14**	**73.7%**	36.9%	8	47.1%	53.4%

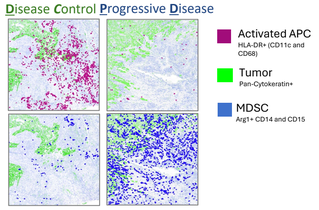
Safety

No concerning or unexpected safety signals identified. *Pepinemab does not add toxicity to pembrolizumab*

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

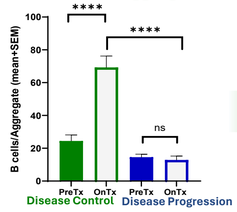
Biologic Activity

Altering the balance of suppressive myeloid to Antigen Presenting Cells



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

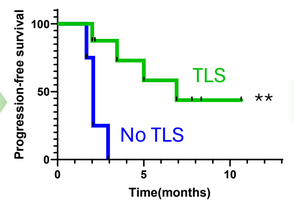
Treatment Induced Mature Immune Aggregates



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. One-way ANOVA, **** p<0.0001; ns = not significant, p≤0.05.

Efficacy

Presence of Mature TLS Correlates with Disease Control

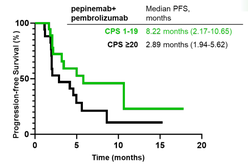


B cell aggregates correlate with PFS. On-treatment biopsies with one or more B cell aggregates positively correlates with longer progression-free survival. N=12 on-treatment biopsies at interim analysis. Log Rank survival statistical analysis resulted in a ** p value of 0.0056.

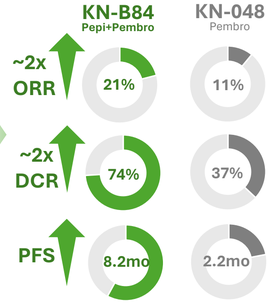
Clinical Benefit in Hard-to-treat Populations

56% of HPV negative "cold tumors" showed induction of TLS after treatment

Progression-Free Survival
Increased in PD-L1 low CPS 1-19



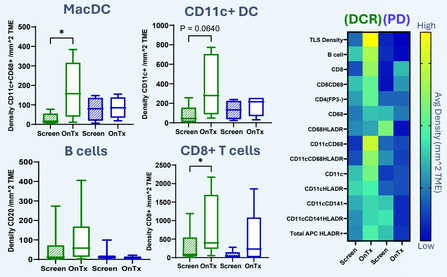
Increased ORR and DCR in Hard-to-treat PD-L1 low



Results

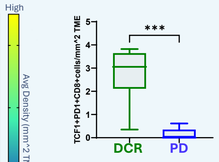
- An increase in the balance of activated APC (HLA-DR+CD11c+ and HLA-DR+CD68+) to suppressive MDSC (Arg1+CD14+ and ARG1+CD15+) was observed in patients with durable disease control.
- Combination therapy induced the formation of highly organized immune aggregates, including a high density of activated B cells, DC's, CD4+ and CD8+ T cells, including stem-like CD8+TCF1+PD1+ T cells.
- Presence of immune aggregates increased in on-treatment compared to pre-treatment biopsies, even in HPV-negative and PD-L1 low tumors.
- Favorable spatial interactions between DC-1, CD8, CD4, and B cells was associated with PFS and disease control.

Treatment Induced Dendritic cells, B cells and T cells within the TME in Disease Control Patients



Disease control patients (DCR include: CR, PR, SD) show an increase in important inflammatory immune cell subsets when treated with pepinemab plus pembrolizumab. MacDc and CD8 T cells had the most significant increase with treatment. Statistical analysis: Two tailed unpaired t test, P<0.05

OnTx Biopsies show higher Stem-Like CD8 in Disease Control



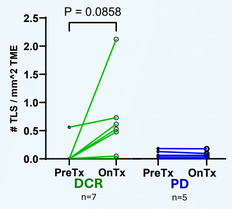
Stem-like CD8 are associated with improved response to immunotherapy and share features with T_{EX} cells found within immune aggregates. Patients with disease control had a higher density of stem-like CD8 T cells after treatment within the TME. Statistical analysis: Two tailed unpaired t test, P<0.05

Disease Control (DCR)
Screen n=17, OnTx n=8

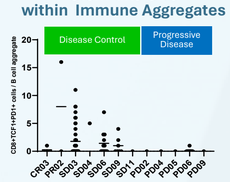
Disease Progression (PD)
Screen n=11, OnTx n=6

Combination therapy induced formation of highly organized immune aggregates with Key Immune Cells for Antigen Presentation and Expansion of T cells

TLS in Matched Biopsy Pairs

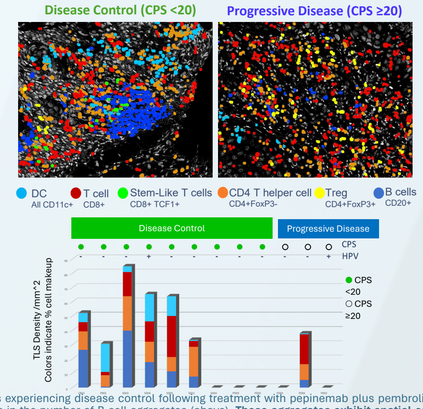


Stem-like CD8 within Immune Aggregates



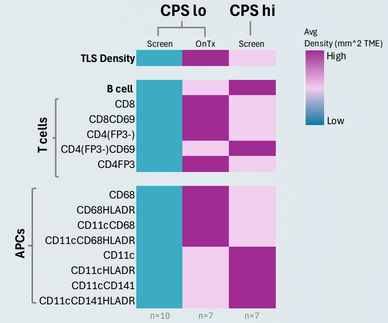
TCF1+PD1+CD8+ Stem-like progenitor cells appear to be associated with Disease Control and located within B cell aggregates

Immune Aggregate Organization



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. **Remarkably, TLS were induced in HPV-negative HNSCC, which typically have low TLS and lower disease control rates.**

Combination Therapy Reprograms Cold Tumors to Hot Tumors, Induces TLS and Correlates with Disease Control



Patients with PD-L1 low (CPS < 20) tumors have lower TLS, B cells, T cells and APCs than PD-L1 high (CPS ≥ 20) disease before treatment. After combination treatment, PD-L1 low patients demonstrate increased density of immune cells needed to mount a robust immune response, including B cells, T cells and APCs, along with an induction of TLS that correlate with durable disease control.

Novel and Independent Mechanism of Pepinemab

Results suggest that combination therapy induced formation of highly organized lymphoid aggregates in HNSCC tumors, with a high density of activated B cells, DC and T cells.

Similar observations in separate trial for patients with metastatic melanoma, supporting that combination immunotherapy with pepinemab induces mature lymphoid structures within the TME[2].

Evidence of treatment-induced biologic activity corresponding with disease control and suggests a novel and independent mechanism of pepinemab to enhance immune interactions and ICI activity.

2024 ASCO ANNUAL MEETING

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8. Fisher et al, Cytometry Part B, 2016; 90B, 199-208
9. Harmonize inclusion / exclusion criteria of KEYNOTE-048 Phase 3 study, reference for historical comparison of single agent KEYTRUDA

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