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Pepinemab a Semaphorin 4D blockade antibody in combination with immune checkpoint therapies **induces mature lymphoid aggregates correlating with clinical outcomes**

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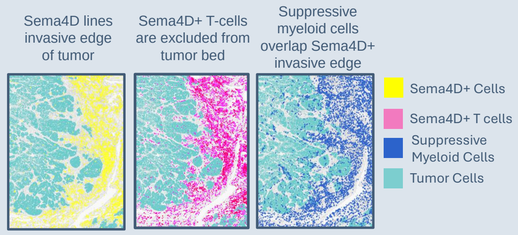
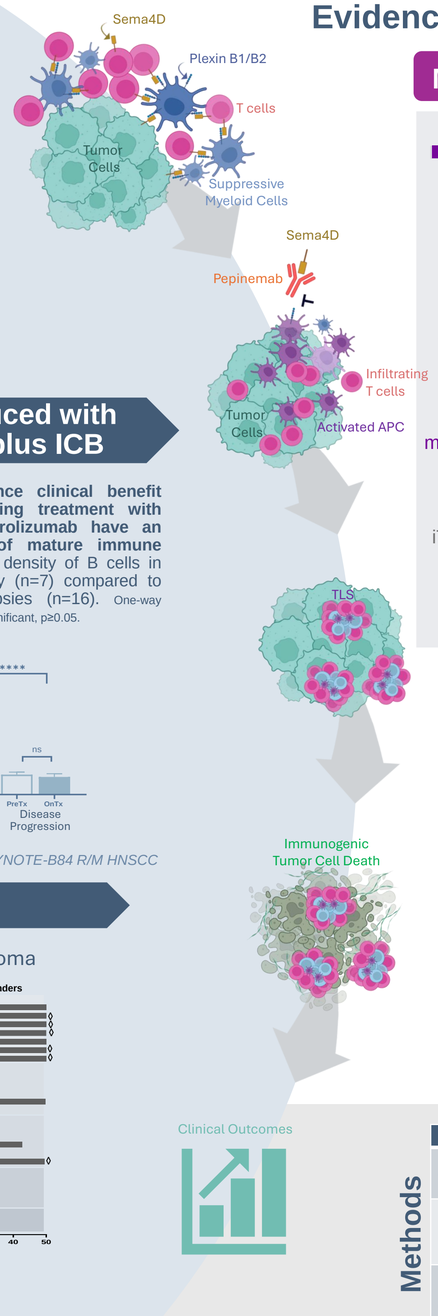
Semaphorin 4D (Sema4D) Immune Suppression

Myeloid cells play a crucial role in suppressing adaptive immunity within the tumor microenvironment (TME). Preclinical studies have shown that semaphorin 4D signaling through its cognate receptors (Plexin B1/B2, CD72) regulates myeloid cell recruitment and suppressive function (doi: 10.1158/2326-6066).



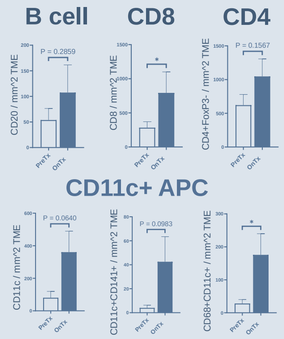
Sema4D regulates myeloid suppression and immune exclusion. Pro-inflammatory cells are excluded from tumor and accumulate at the tumor invasive edge. CD8 and CD4 T cells are excluded from the tumor bed and many express Sema4D. SEMA4D signaling through receptors on myeloid cells promotes immune suppression, restricting T cells from entering tumor at the invasive edge. *Human untreated tumor from neoadjuvant HNSCC NCT03690986.*



Sema4D Blockade reverses Immune Suppression

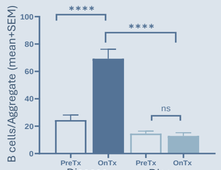
When SEMA4D is blocked from binding to its receptors, suppression is reduced, leading to increased penetration and organization of antigen presenting cells (APC) and lymphoid cells in the TME. This immune cell composition including APC and CD4 would be expected to facilitate productive interactions to empower CD8+ T cells, accounting for improved immune responses in otherwise "cold" tumors.

We hypothesized that pepinemab may increase lymphoid aggregates within “cold” tumor populations, including HPV-negative and PD-L1 low HNSCC to enhance activity of immune checkpoint blockade (ICB).



TLS are induced with pepinemab plus ICB

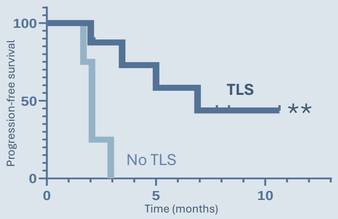
Patients who experience clinical benefit (Disease Control) during treatment with pepinemab and pembrolizumab have an increased frequency of mature immune aggregates with a high density of B cells in their on-treatment biopsy (n=7) compared to their pre-treatment biopsies (n=16). One-way ANOVA, **** p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



KEYNOTE-B84 R/M HNSCC

TLS correlate with Improved Clinical Response

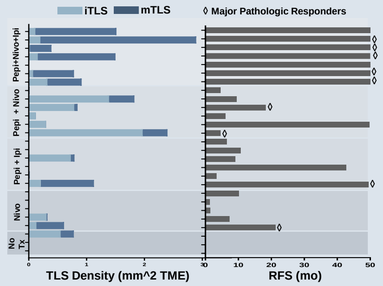
TLS correlate with PFS in R/M HNSCC



B cell aggregates correlate with progression-free survival (PFS). On-treatment biopsies with one or more B cell aggregate (≥20 CD20+ cells within 50um of each other) positively correlate with longer progression-free survival. n=8 TLS, n=4 no TLS on-treatment biopsies at interim analysis. Log Rank survival statistical analysis resulted in a ** p value of 0.0056.

KEYNOTE-B84 R/M HNSCC

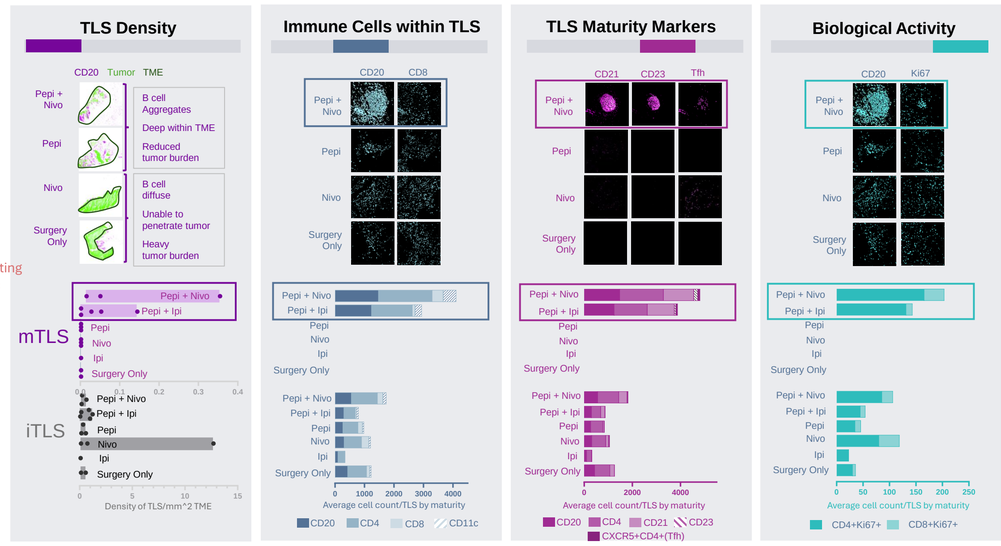
mTLS correlate with RFS Melanoma



Increased maturity of TLS correlating with improved recurrence-free survival (RFS) in Melanoma with Pepi+Nivo+Ipi treatment. TLS maturity by patient stratified by treatment. Immature TLS (iTLS) classified as aggregates of >20 CD20+ B cells with CD4+ T cells. Mature TLS (mTLS) classified as TLS aggregates containing maturity markers CD21+ follicular DC and/or CD23+ germinal center B cells. Recurrence-free survival (RFS) in months with major pathologic responders demarcated. *Neoadjuvant Melanoma NCT03769155*

Evidence of efficacy in Hard-to-treat populations

Mature TLS induced in HPV-negative HNSCC

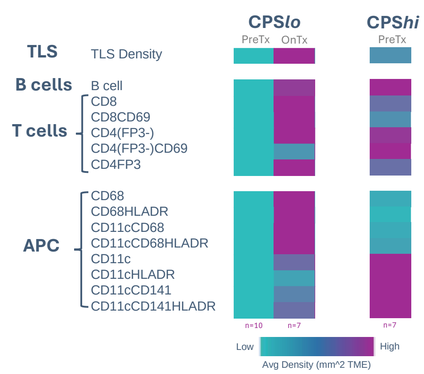


A higher frequency of mature TLS were observed in tumors treated with pepinemab in combination with either Nivolumab or Ipilimumab over single immune therapies. Enhanced maturity stratified using TLS maturity markers:

- B cell aggregates >20 cells
- T cell zone
- Follicular DC (CD21+)
- Germinal center B cells (CD23+)
- T follicular helper (CXCR5+CD4+)
- Proliferation (Ki67+) within TLS suggests biological activity.

Quantification of biomarkers, showing increased density of mature TLS (mTLS) with Pepi in combination with ICB. Average immune cell and maturity marker cell densities by treatment group. Biological activity shown using Ki67+ proliferating B and T cells within the TLS. Note: Analysis shown for HPV- patient biopsies, which tend to lack or have vastly reduced TLS and immune infiltration, relative to HPV+ HNSCC. Pepi+Nivo (n=3), Pepi+Ipi (n=5), Pepi (n=3), Nivo (n=3), Ipi (n=1), Surgery (n=2).
Neoadjuvant HNSCC NCT03690986

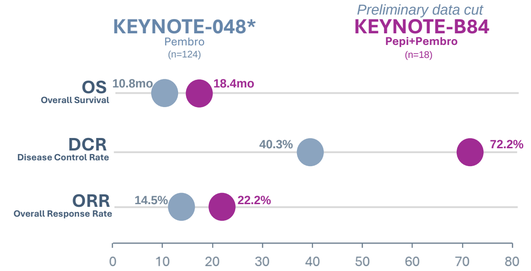
Increased outcomes in PD-L1 (CPS) low



Changes balance from “cold” to “hot” TME in hard-to-treat PD-L1 low patients

Patients with disease control (CR, PR, SD) with PD-L1 low (CPS < 20) tumors are relatively cold compared to PD-L1 high (CPS ≥20). CPS low tumors have lower density of TLS, B cells, T cells and APCs than CPS high disease before treatment. After combination treatment, CPS low patients demonstrate increased density of immune cells characteristic of a robust immune response, including B cells, T cells and APCs. *KEYNOTE-B84 HNSCC.*

Clinical Responses ~2X increase in PD-L1 low



Increased ORR, DCR, and OS in Hard-to-treat PD-L1 low patients (CPS 1-19).
KEYNOTE-B84 HNSCC

- Burtness et al, **Pembrolizumab alone for R/M HNSCC (KEYNOTE-048).** *Lancet,* 2019. **Subgroup analysis by PD-L1 CPS.** *JCO,* 2022.
- NOTE: These are preliminary data, reported prior to DBL.

Clinical Outcomes

Methods

Trial	Inclusion	Treatment Cohorts	End-points	Status
KEYNOTE-B84 (NCT04815720)	First-line, IO naïve, R/M HNSCC	pepinemab + pembrolizumab	Safety and efficacy	Ongoing N=49
Biomarker neoadjuvant HNSCC (NCT03690986)	surgically resectable HNSCC	pepinemab pepinemab + nivolumab Pepinemab + ipilimumab nivolumab alone or ipilimumab alone	Biomarker analysis	Ongoing N=6 per cohort
Biomarker neoadjuvant Melanoma (NCT03769155)	Metastatic melanoma, surgically resectable	pepinemab + nivolumab + ipilimumab pepinemab +nivolumab pepinemab + ipilimumab nivolumab alone	Biomarker analysis	Manuscript in progress N=8 per cohort

Screening and on-treatment biopsies were collected. Biomarker analyses included the evaluation of tumoral immune cells using multiplex immunohistochemistry (mIHC) assessing up to 36 markers per biopsy. Unbiased algorithms identified co-localized markers for advanced cell phenotyping, density, spatial, and proximity analysis using Visiopharm image analysis software. Biomarker results were then stratified by clinical outcome measures.

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