2025 ASCO ANNUAL MEETING

Neoadjuvant biomarker trial of pepinemab to enhance nivolumab or ipilimumab activity in resectable head and neck cancer.

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Key Takeaway Points/Conclusions

HNSCC UNMET NEED

Immunotherapy is now standard care for metastatic head and neck squamous cell carcinoma (HNSCC). Growing evidence supports the use of immune checkpoint inhibitors (ICI) in neoadjuvant and adjuvant settings.

Resistance to ICI remains a challenge, driven by:

- **Abundance of Myeloid-derived suppressor cells** (MDSCs) and lack of activated DC
- **Exclusion of effector immune cells** from the tumor microenvironment

OVERCOME RESISTANCE

Blocking SEMA4D from binding its receptors on myeloid cells:

- **reprograms myeloid-driven immunosuppression**
- **induces formation of mature tertiary lymphoid structures (mTLS),** a biomarker associated with improved response to ICI and durable clinical benefit

Neoadjuvant treatment with **pepinemab, a semaphorin 4D (SEMA4D) blocking antibody** and/or ICI was evaluated in patients with resectable disease.

EFFICACY WITHOUT INCREASED TOXICITY

Pepinemab offers a **novel and well-tolerated** approach to **mitigate immunotherapy resistance** and enhance ICI efficacy in the neoadjuvant treatment setting.

- **PK as expected**
- **No unexpected TRAEs**
- **Mature TLS in patients treated with pepinemab combined with ICI were associated with pathologic response**

PRESENTED BY: Conor E. Steuer, MD. Associate Professor, Emory University

Background

Head and neck squamous cell carcinoma (HNSCC)

Prevalence

Head and neck squamous cell carcinoma (HNSCC) is the **seventh most common** cancer worldwide, representing 4.5% of cancer deaths

Current roadblocks

The majority of HNSCC presents with localized, potentially curative disease. Treatment is generally **toxic** including **large surgeries, chemotherapy and radiation**

Current therapies

Immunotherapy is a standard of care in the metastatic setting, and recent data from **KEYNOTE 689** and **NIVOPOSTOP GORTEC 2018-01** has demonstrated **benefit for immunotherapy** in the **neoadjuvant/adjuvant** setting

Despite these advances, most patients either do not respond to immunotherapy and further research is needed to improve outcomes for this patient population

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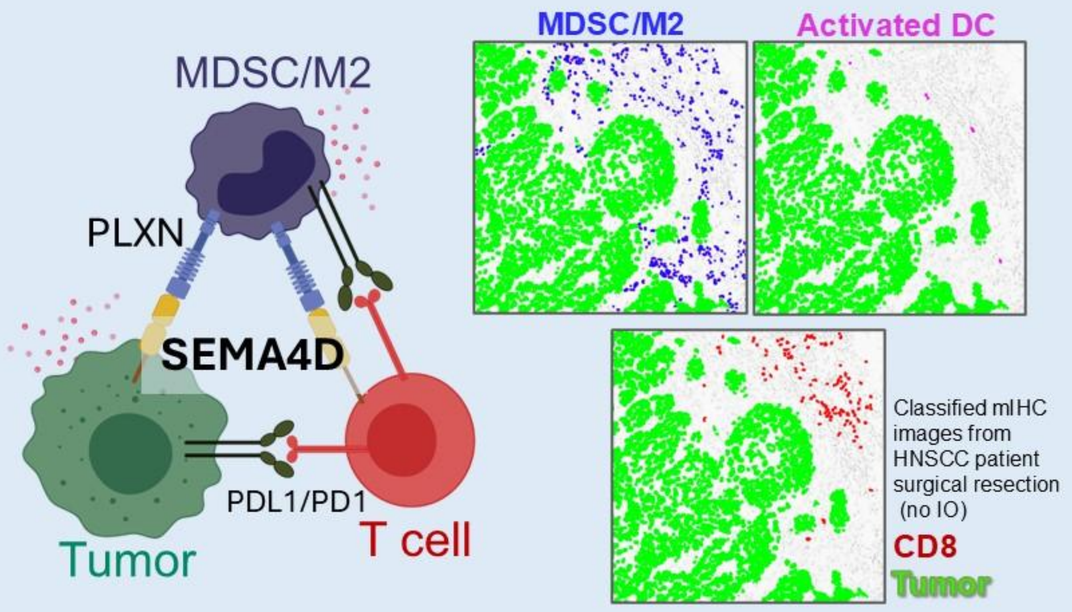
Background

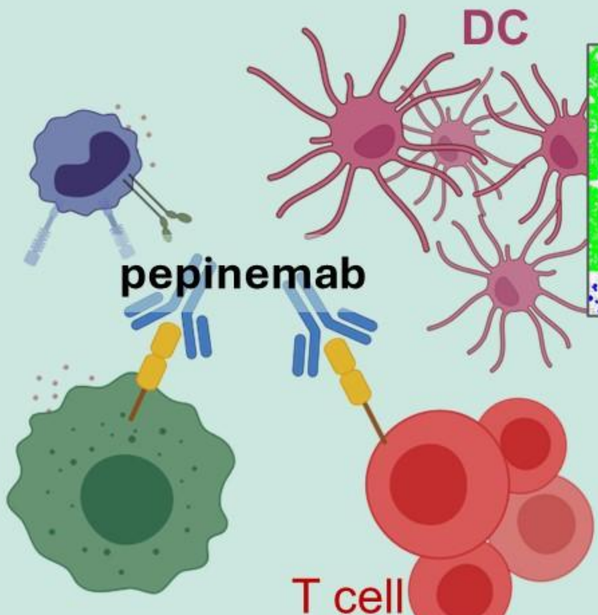
Pepinemab reverses myeloid suppression and promotes activation of DC in the tumor microenvironment (TME)

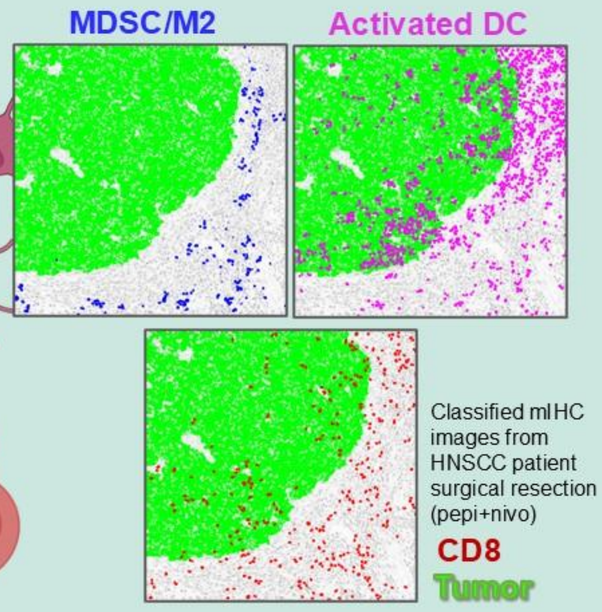
The TME of head and neck cancer (HNSCC) is “cold” and resistant to Immune checkpoint Inhibitors (ICI)
Semaphorin 4D (SEMA4D) promotes myeloid suppression



- Abundant Myeloid Suppressor Cells (MDSC)
- T cell exclusion

Pepinemab, a SEMA4D blocking antibody,
reverses myeloid suppression and
promotes activation of Dendritic Cells(DC) to enhance ICI





- ↑ Activated Dendritic Cells (DC):MDSC ratio
- ↑ T cell infiltration

Immunosuppressive

Inflammatory

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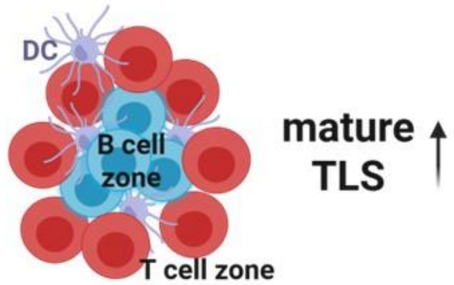
Background

Pepinemab ***induced*** TLS when combined with pembrolizumab and correlated with improved survival in R/M HNSCC

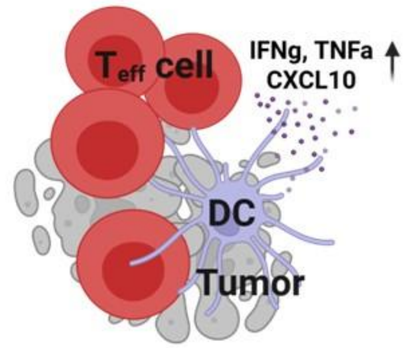
Induction of TLS

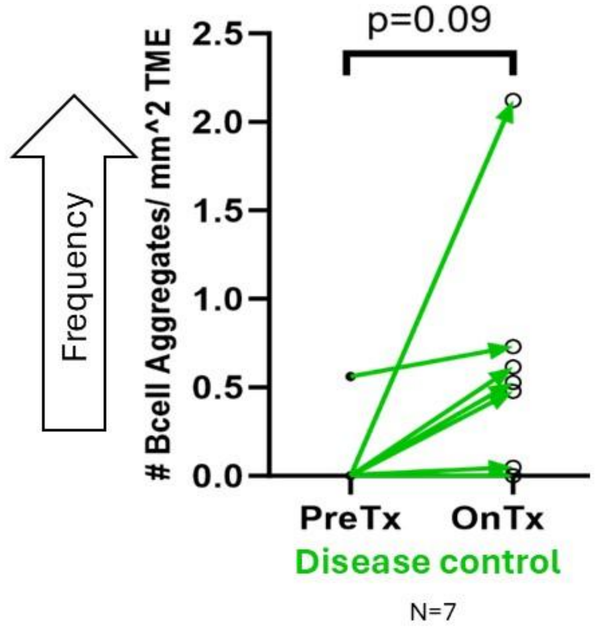
Pepinemab recruits and activates DC to organize lymphocytes into TLS forming robust immune communication centers



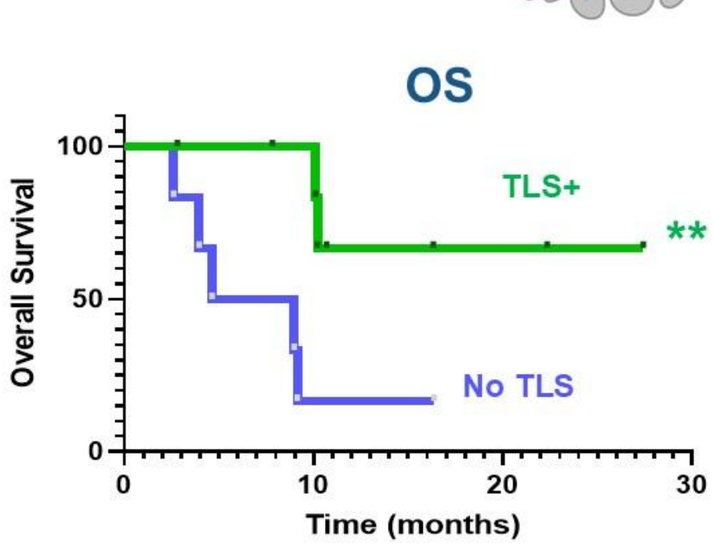
Improved clinical benefit

Enhance efficiency of ICI by overcoming resistance mechanisms in the TME





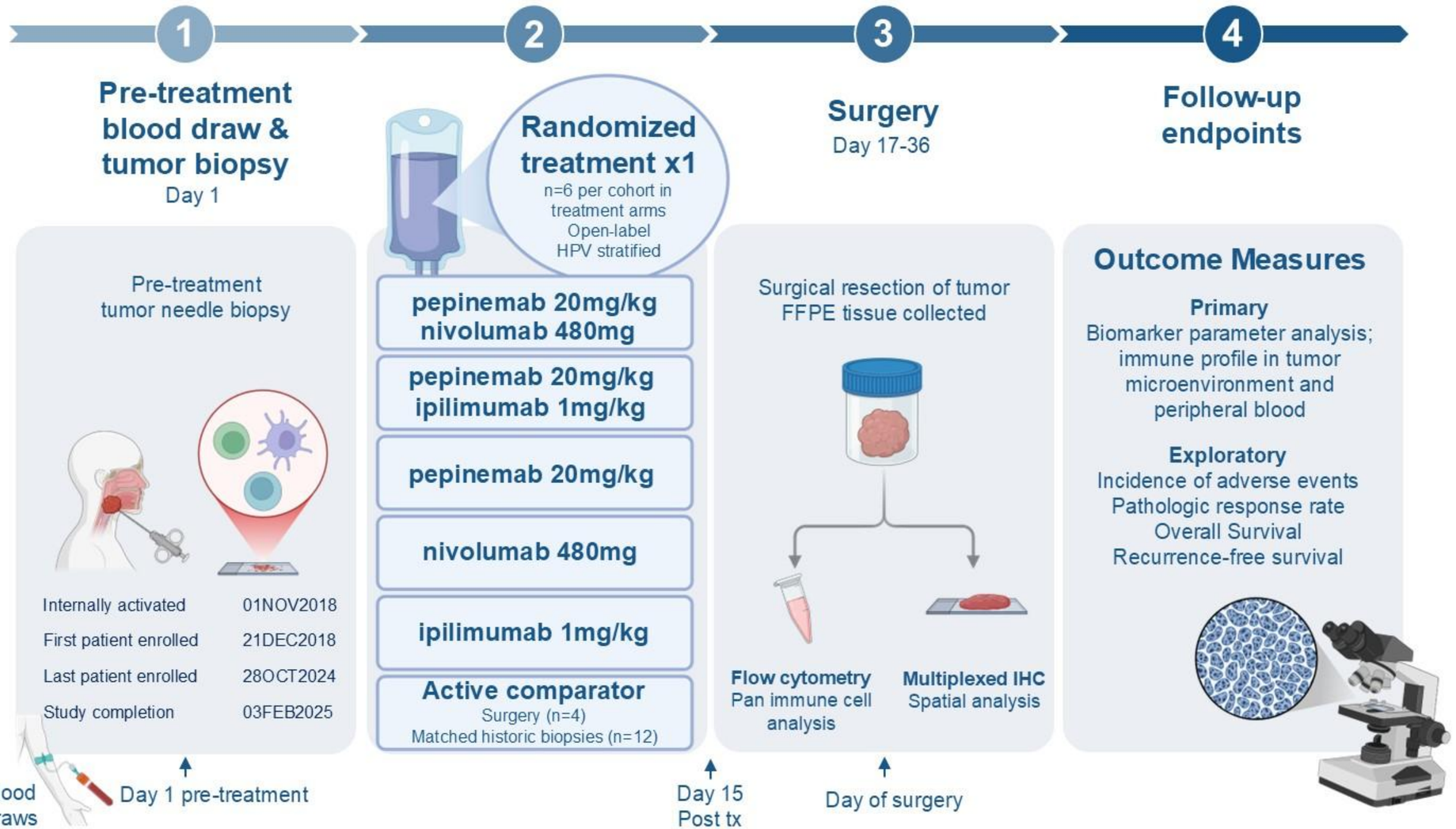
High density of TLS following treatment correlate with durable clinical benefit



KEYNOTE-B84: Patients with R/M HNSCC were treated with pepinemab + pembrolizumab

Methods

Neoadjuvant treatment of pepinemab in combination with ipilimumab or nivolumab in patients with head and neck cancer (NCT03690986)



Demographics

Covariate	Treatment						
	Ipilimumab	Nivolumab	No Treatment (Surgery Alone)	Pepinemab	Pepinemab + Ipilimumab	Pepinemab + Nivolumab	P-value**
	N=6	N=6	N=4	N=6	N=6	N=6	
Age							**0.291***
Mean (Std Dev)	66.7 (8.9)	65.3 (10)	61 (6.1)	64 (8.4)	60.2 (14.4)	56 (6.1)	
Median (Q1-Q3)	68.5 (61-75)	65 (62-74)	62 (56.5-65.5)	62.5 (58-70)	65 (54-70)	57.5 (52-60)	
Min - Max	52-75	49-77	53-67	54-77	34-73	46-63	
Sex | N (%)							**0.732***
F	1 (20)	2 (33.3)	0 (0)	2 (33.3)	1 (16.7)	3 (50)	
M	4 (80)	4 (66.7)	4 (100)	4 (66.7)	5 (83.3)	3 (50)	
N missing	1	0	0	0	0	0	
Race/ Ethnicity | N (%)							**0.151***
A/NH	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	
B/NH	0 (0)	2 (33.3)	0 (0)	0 (0)	1 (16.7)	0 (0)	
W/H	0 (0)	0 (0)	0 (0)	3 (50)	1 (16.7)	0 (0)	
W/NH	5 (83.3)	4 (66.7)	4 (100)	3 (50)	3 (50)	5 (83.3)	
unk	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor Site | N (%)							**1***
Oral Cavity	4 (80)	4 (80)	3 (75)	4 (66.7)	5 (83.3)	5 (83.3)	
Oropharynx	1 (20)	1 (20)	1 (25)	2 (33.3)	1 (16.7)	1 (16.7)	
N missing	1	1	0	0	0	0	
HPV p16 | N (%)							**1***
Neg	5 (83.3)	5 (83.3)	3 (75)	4 (66.7)	5 (83.3)	5 (83.3)	
Pos	1 (16.7)	1 (16.7)	1 (25)	2 (33.3)	1 (16.7)	1 (16.7)	
N missing	0	0	0	0	0	0	

** The p-value is calculated by either parametric (ANOVA, Chi-squared) or non-parametric (Kruskal-Wallis, Fisher's exact) test, where appropriate, based on the normality test of data distribution and the sample size.

* A non-parametric test (Kruskal-Wallis or Fisher's exact test) is applied.

Treatment related adverse events

- No unexpected adverse events
- Very low frequency of Grade 3-4 events and no Grade 5 events
- All patients proceeded to surgery without delays

Adverse Events	ipilimumab N=6		nivolumab N=6		no IO N=4		pepinemab N=6		pepinemab + ipilimumab N=6		pepinemab + nivolumab N=6	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
Total Subjects with any Event	1 (16.7)	**0**	1 (16.7)	**0**	0	**0**	2 (33.3)	**0**	2 (33.3)	**0**	4 (66.7)	**1 (16.7)**
Back pain	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**	0	**0**	0	**0**
Chills	0	**0**	0	**0**	0	**0**	2 (33.3)	**0**	0	**0**	0	**0**
Diarrhea	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**	0	**0**	1 (16.7)	**0**
Fatigue	1 (16.7)	**0**	0	**0**	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**
Insomnia	0	**0**	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**	0	**0**
Rash maculo-papular	0	**0**	0	**0**	0	**0**	0	**0**	1	**0**	1 (16.7)	**0**
Blood and lymphatic system disorders	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	1 (16.7)	**1 (16.7)**
Musculoskeletal and connective tissue disorder - Other, specify	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**
Neck pain	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	1 (16.7)	**0**
Hyperglycemia	0	**0**	1 (16.7)	**0**	0	**0**	0	**0**	0	**0**	0	**0**
Neck edema	0	**0**	1 (16.7)	**0**	0	**0**	0	**0**	0	**0**	0	**0**

Evaluation of pathologic tumor response following neoadjuvant treatment

Exploratory endpoint

	Combination ICI TX	Single ICI TX	ALL ICI	NO ICI SOC
n	12	18	30	16 (4+12†)
TR1	2	3	5	1
TR2	4	4	8	0
TR2%	33.3%	22.2%	26.7%	0%
mPR	2	1	3	0
%mPR	16.7%	5.5%	10%	0%

Pathological criteria for tumor response (TR)*:

- **TR0**: <10% tumor response
- **TR1**: between 10% and 49% tumor response
- **TR2**: ≥50% tumor response
- **mPR:** >90% tumor response

By blinded independent pathologist review

** Uppaluri et al. 2020 Clin Can Res*

While the study was not powered to evaluate clinical efficacy, our findings support that neoadjuvant IO appears to improve mPR rate in HNSCC

- 9.4% mPR reported for KEYNOTE-689 pembrolizumab peri-operative treatment ($p<0.0001$; n=714)

† matched historic surgical resections

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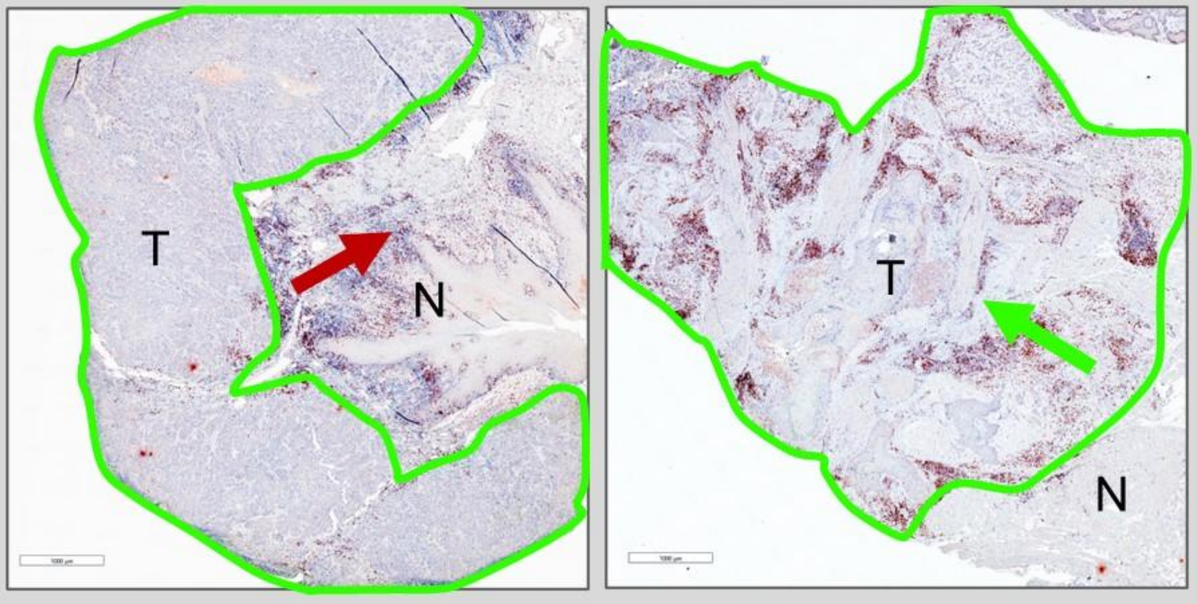
Pepinemab increased infiltration of T cells and B cells

Biomarker Results: Primary Endpoint

T cells

T cells are excluded

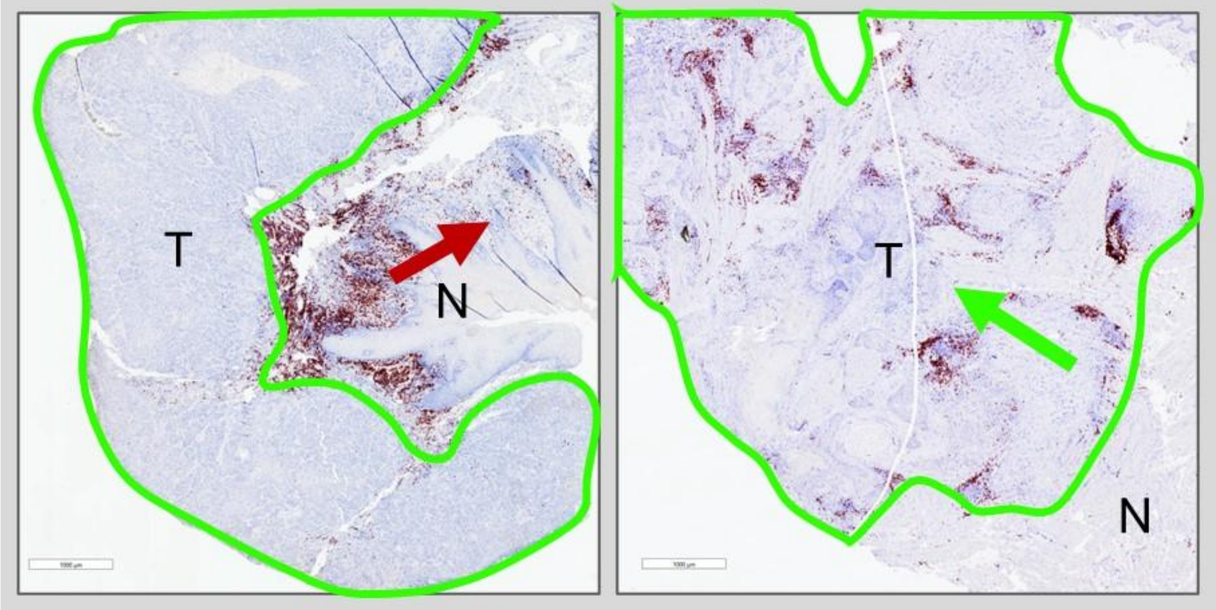
Pepinemab increases **CD8+ T cell** penetration



B cells

B cells are excluded

Pepinemab increases **B cell** penetration



TME border T = Tumor N = Normal adjacent

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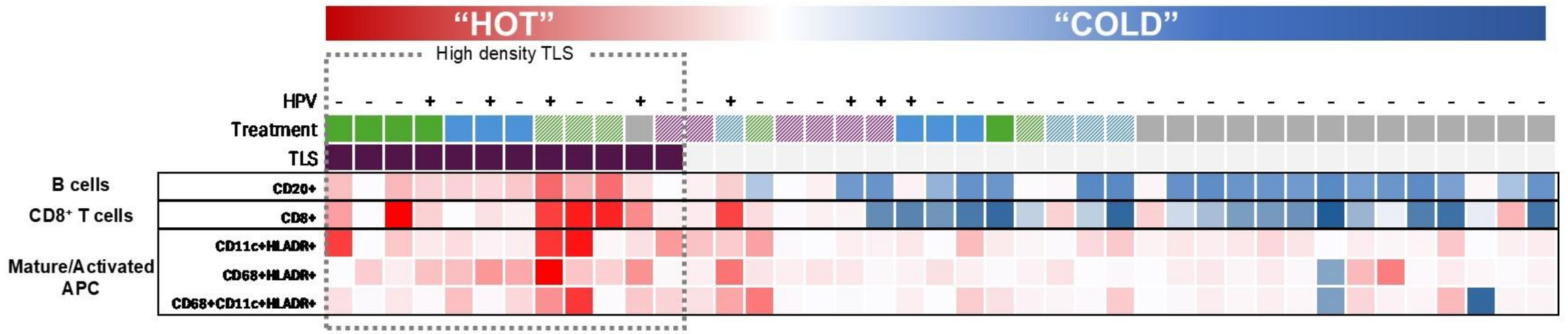
Immunotherapy treatment is associated with TLS which correlates with a pro-inflammatory or 'hot' TME

Biomarker Results: Primary Endpoint

Cellular densities within the TME (mIHC heatmap)



Overall cellular densities within surgical resection tissues reveal that **activated APCs** **along with elevated B cells, CD8⁺ T cells are associated with organization of high density TLS following IO treatment.**

Treatment
- pepi+nivo
- pepi+ipi
- pepi
- nivo
- ipi
- untreated

TLS Density
- TLS high density
- no TLS/ low TLS

Cell density (mm^2 TME) analyzed by mIHC

CD20/CD8

High 4500 392 0 Low

450 1.7 0

APC

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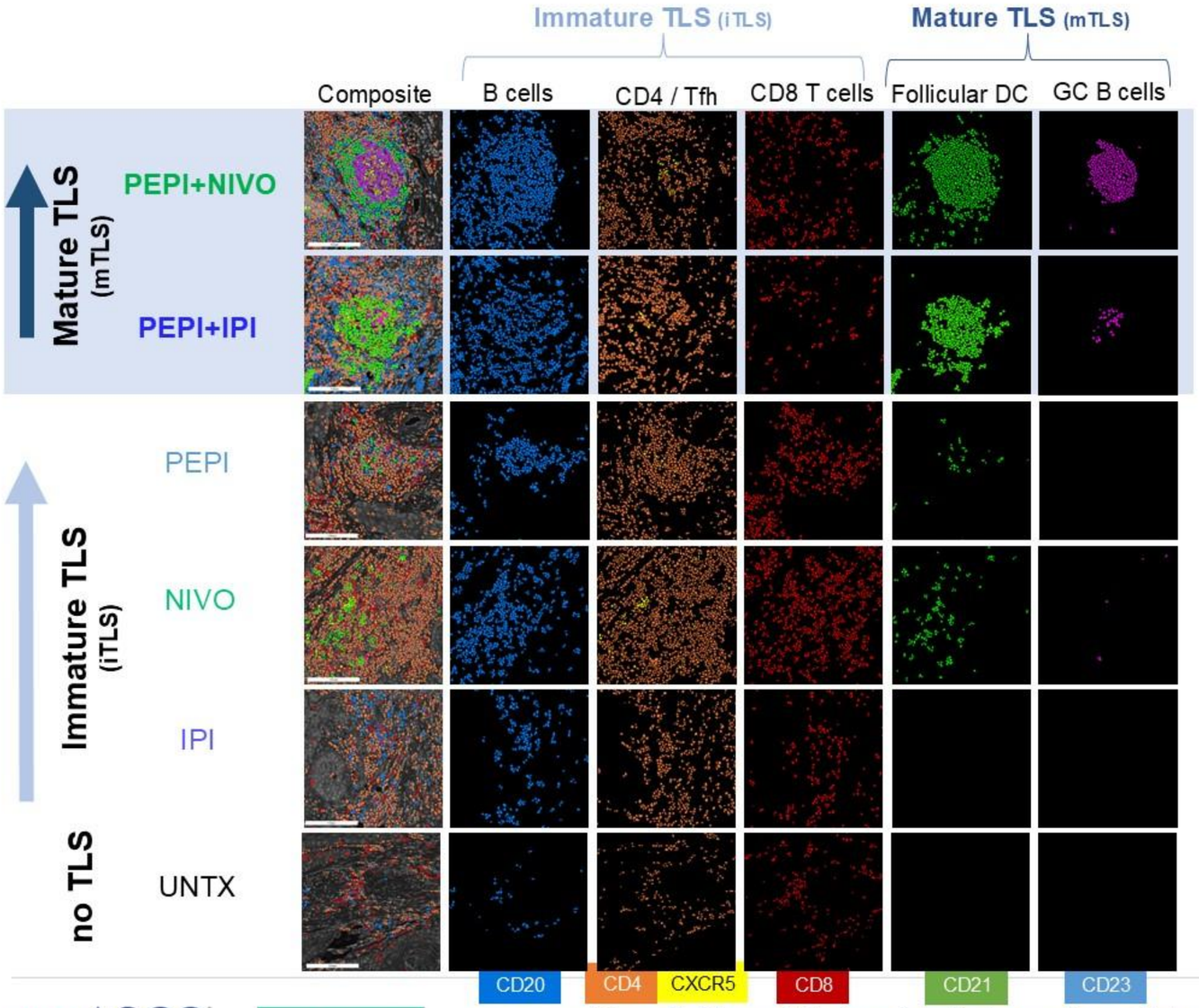
Pepinemab plus ICI significantly increased density of intra-tumoral mature TLS

Biomarker results: primary endpoint



High density of mature TLS with Combination ICI

	PEPI+ NIVO	PEPI+ IPI	PEPI	NIVO	IPI	NO IO#
mTLS	**3/5 60%***	**3/6 50%***	0/6 0%	1/5 20%	0/4 0%	1/16 6.3%

- mTLS form germinal centers (GC) and contain follicular DC and GC B cells
- mTLS are reported to be associated with response to ICI and durable clinical benefit
- **High density of mTLS were observed in majority of patients treated with combination of pepinemab + nivolumab or pepinemab + ipilimumab**

* $p<0.05$, compared to No IO, Fisher's exact test

#No IO includes 12 patients from correlative study

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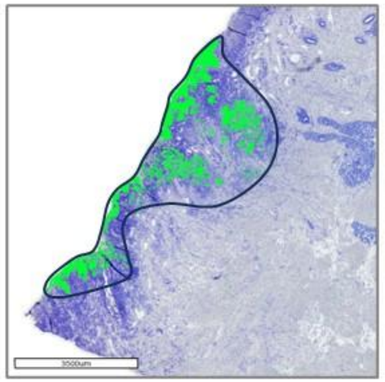
Mature TLS Correlate with Improved Pathologic Response

Biomarker results: primary endpoint stratified by tumor response

TR0 < 10% tumor response



TR1 = 10-49% tumor response

TR2 ≥50% tumor response

Representative images from pepi+nivo treatment arms

TME Viable tumor

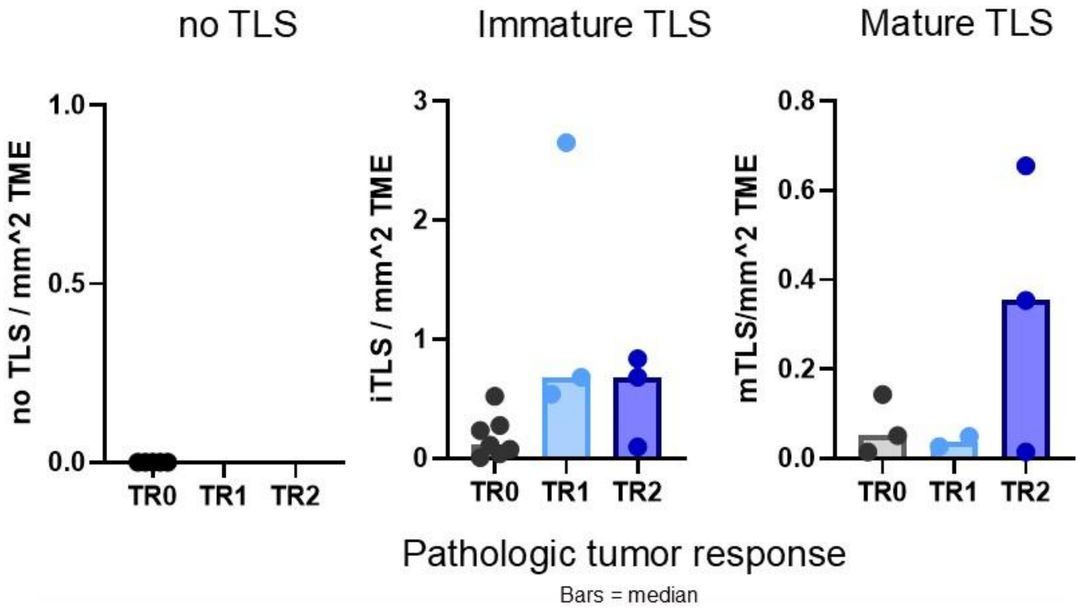
Pathological criteria for tumor response (TR)*:

- **TR0**: <10% tumor response
- **TR1**: between 10% and 49% tumor response
- **TR2**: ≥50% tumor response

By blinded independent pathologist review

** Uppaluri et al. 2020 Clin Can Res*

Abundant and mature TLS are associated with Pathological Response



- All resected tumors with NO TLS were TR0
- iTLS associated with TR1 & TR2
- **mTLS are highly associated with TR2**

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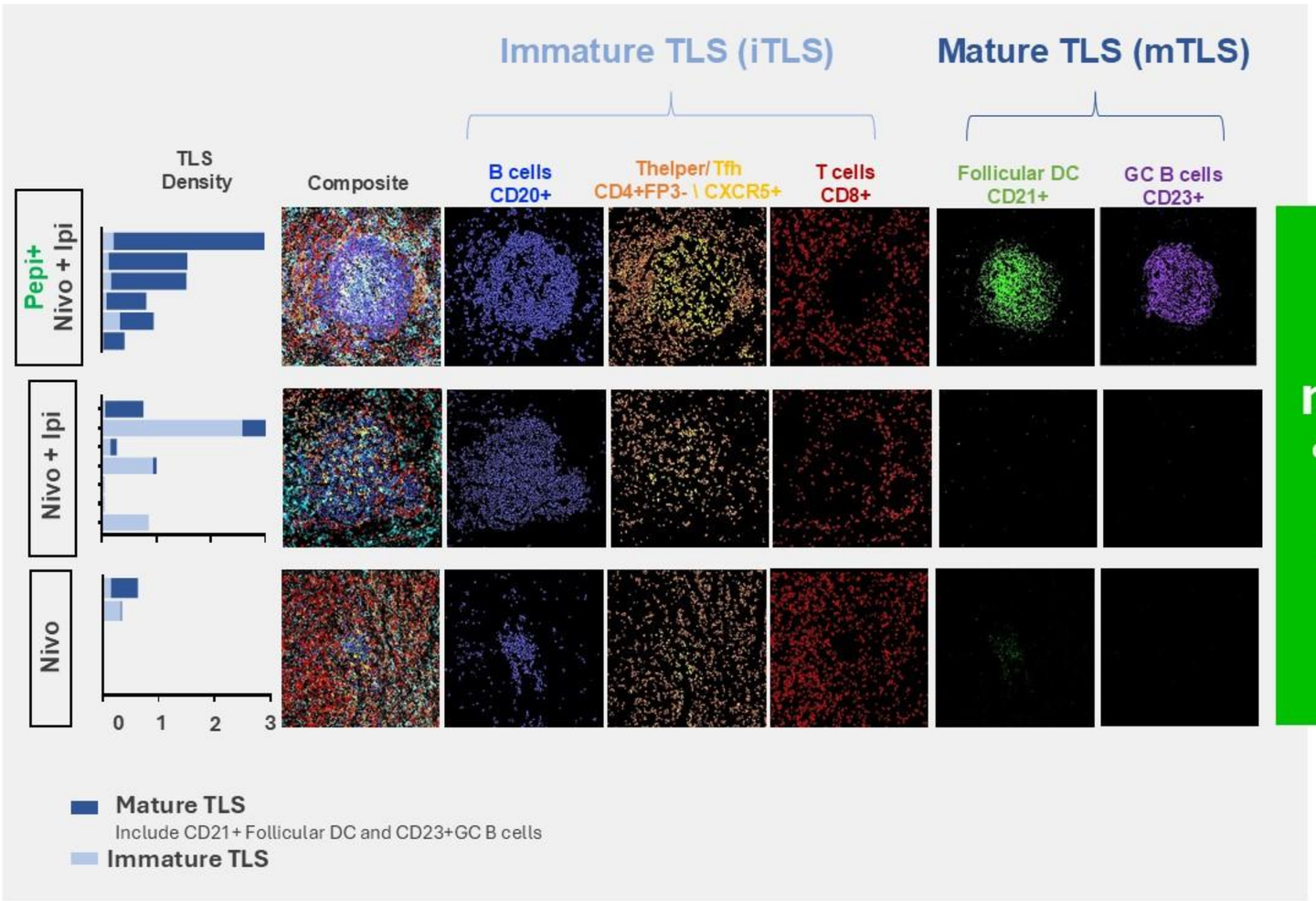
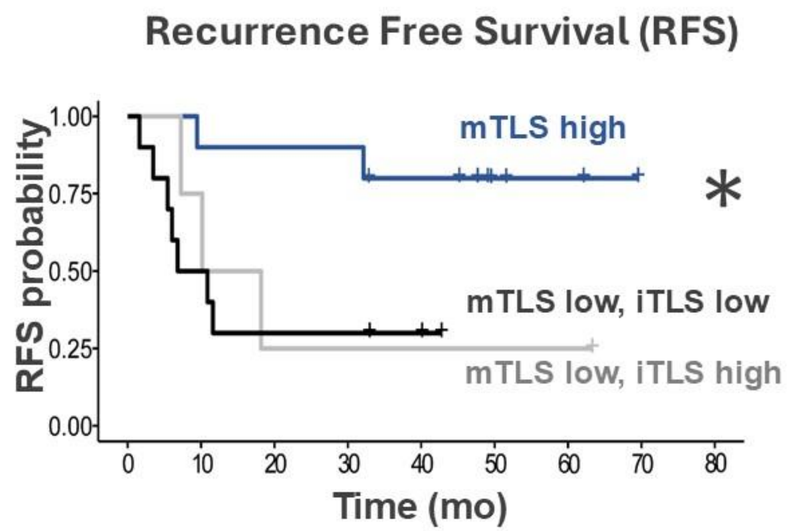
Pepinemab promotes formation of mTLS, which are associated with improved clinical outcomes in patients with resectable melanoma

Efficacy in neoadjuvant melanoma



mTLS correlate with RFS



Median duration of follow up = 50 months

Neoadjuvant trial in Stage III Melanoma. collaboration with Emory University (NCT03769155) and with Jennifer Wargo at MD Anderson Cancer Center (MDACC)

Ruffin et al, submitted 2025

Summary & future directions

HNSCC	Growing evidence supports IO use in **neoadjuvant** and adjuvant settings for head and neck squamous cell carcinoma (HNSCC). Resistance to IO remains a challenge in treatment of HNSCC.
OVERCOMING RESISTANCE	**Pepinemab** offers a **novel and well-tolerated** approach to **mitigate immunotherapy resistance** due to myeloid suppression and exclusion of effector immune cells from TME **and enhance immune checkpoint inhibitor (ICI)** efficacy in the neoadjuvant treatment setting. • **No unexpected TRAEs** • **Reprograms myeloid-driven immunosuppression toward DC activation** • **Induces formation of mature tertiary lymphoid structures (mTLS)** • **Higher density, mature TLS formation in patients treated with pepinemab is associated with pathologic response.**

STUDY LIMITATIONS	• This small biomarker study confirmed association between pepinemab-induced TLS and pathologic responses
	• Correlations with clinical survival endpoints are limited by:
	  • small heterogeneous cohorts
	  • a gap in enrollment period due to COVID
	  • premature follow up period
	• A larger trial with longer follow up time is needed.
	• Additional combinations may further improve efficacy.

CONCLUSIONS	Pepinemab represents a **promising and tolerable** new strategy to overcome resistance mechanisms and enhance ICI in the neoadjuvant setting.

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THANK YOU

to the

PATIENTS & FAMILIES

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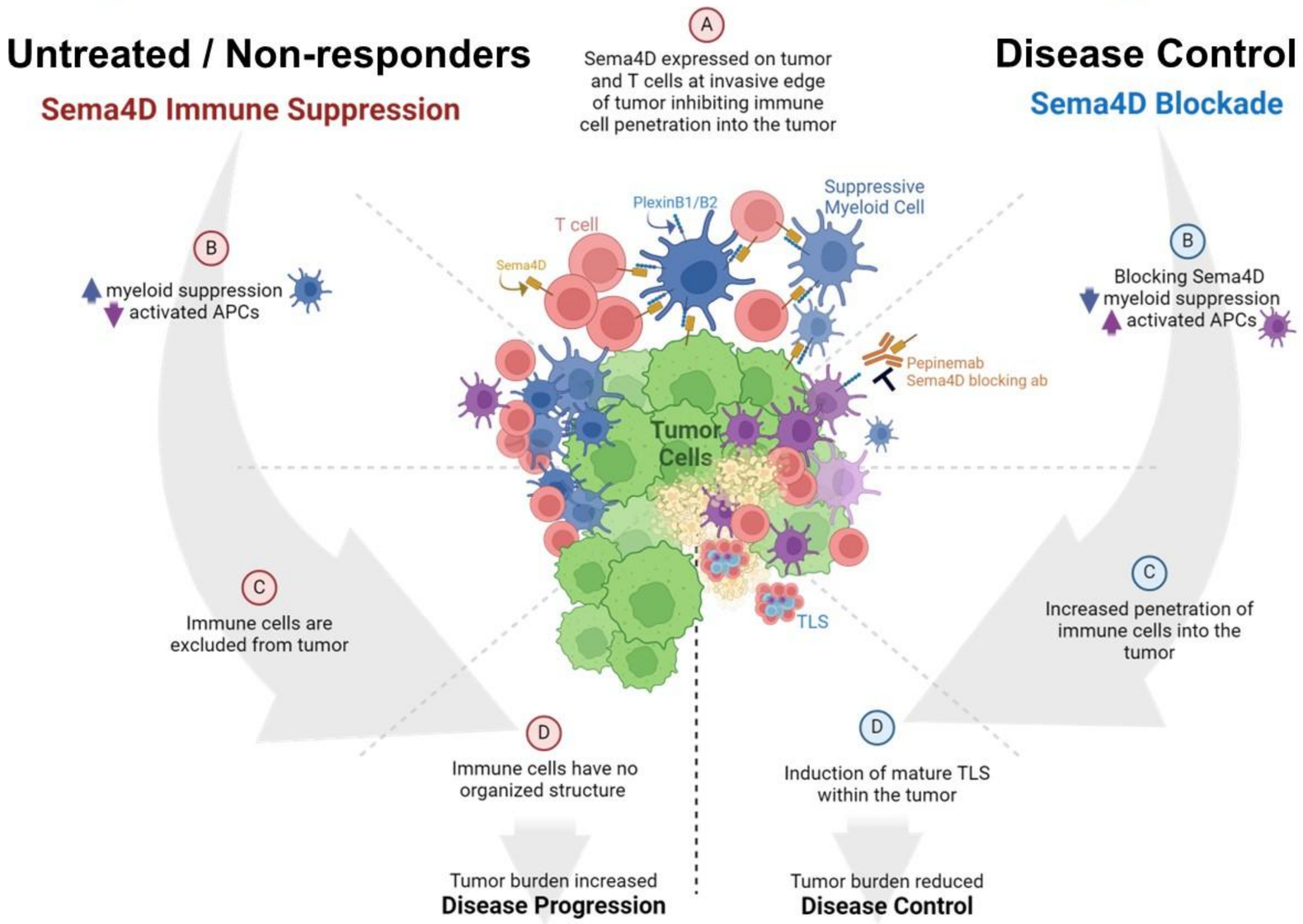
Pepinemab, SEMA4D blocking antibody



1. Turns "cold" hard-to-treat TME "hot"
2. Induces mature TLS in HPV^{neg} hard-to-treat HNSCC tumors unprecedented
3. Mature TLS correlates with better outcome and reduced tumor burden
4. Evidence in neoadjuvant Melanoma, neoadjuvant HNSCC, and metastatic HNSCC in combination with ICI

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