Neoadjuvant pepinemab enhances immune checkpoint blockade in metastatic melanoma

characterized by biomarkers of TME reprogramming including tertiary lymphoid structures

Crystal Mallow
Vaccinex, Inc.
in collaboration with Emory University and
MD Anderson Cancer Center

40TH ANNIVERSARY
Society for Immunotherapy of Cancer
SITC 2025
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Disclosures

Crystal Mallow

Current Employee of Vaccinex, Inc.

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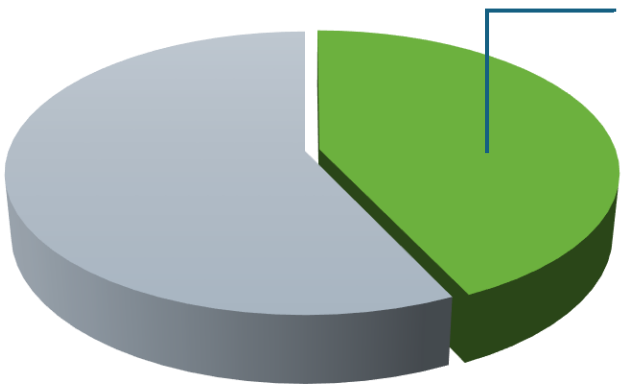
Clinical Need & Rationale

Neoadjuvant immunotherapy in metastatic melanoma

10 Year overall survival



43%

nivolumab + ipilimumab

CheckMate 067 Trial

DOI: 10.1056/NEJMoa2407417

Neoadjuvant immunotherapy is a major advance in management of **metastatic melanoma**

However, **resistance and recurrence** remain major clinical challenges

- Many patients either fail to respond
- Or develop resistance over time

Novel and safe combinations are needed to add to the foundation established in trials such as CheckMate067 to **improve efficacy without added toxicities**

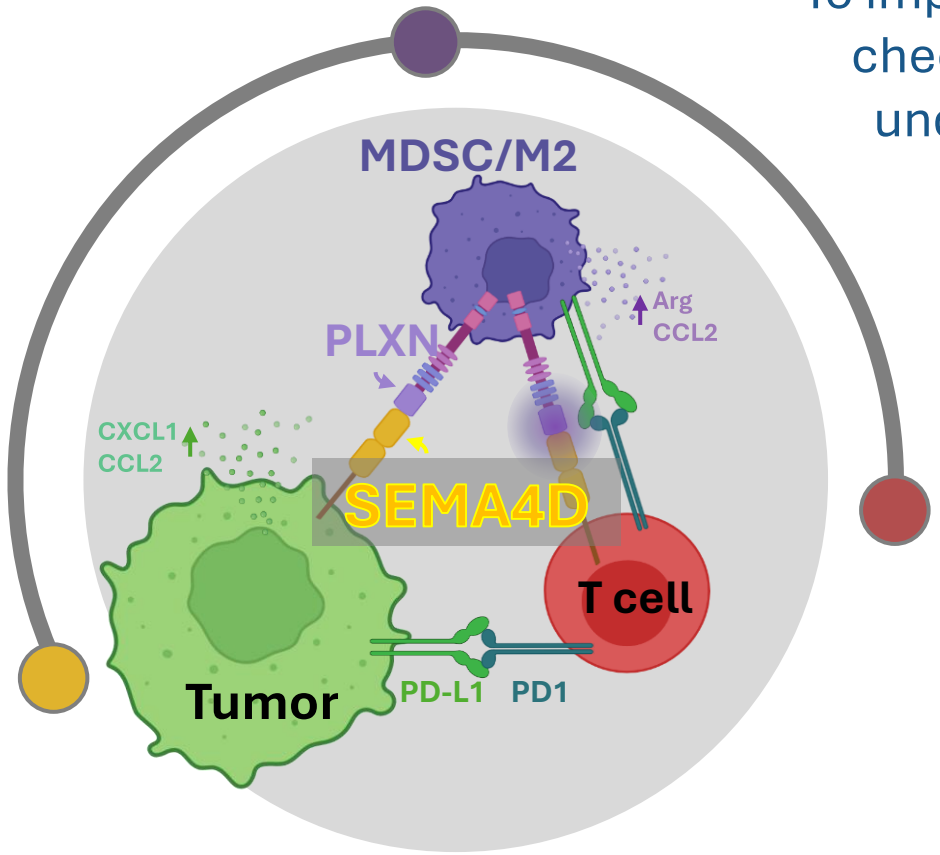
Semaphorin 4D (SEMA4D) drives myeloid immunosuppression

a key resistance mechanism to ICI in the tumor microenvironment (TME)

SEMA4D expressed on tumor and T cells
at tumor periphery

Suppressive myeloid cells express receptors PlexinB1/B2
Receptor engagement promotes myeloid recruitment and induces suppressive function

Inhibits T cell function and penetration into the tumor bed



To improve outcomes with immune checkpoint inhibitors, we must understand the mechanisms driving resistance.

Semaphorin 4D (SEMA4D) drives myeloid immunosuppression

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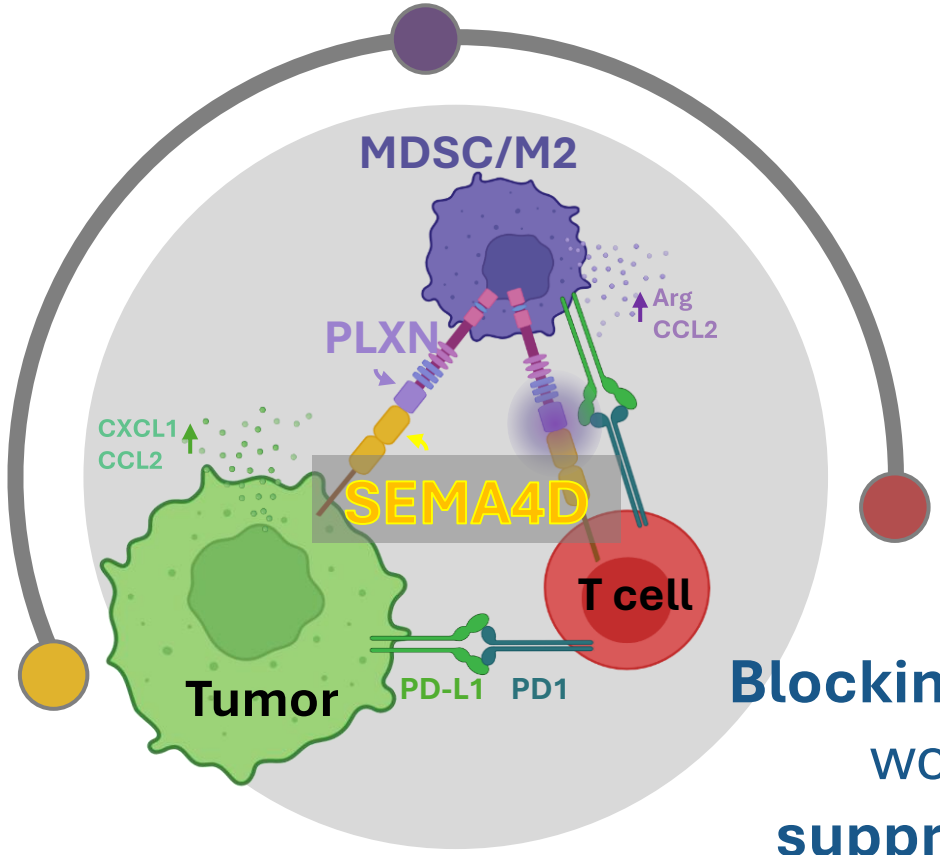


We hypothesized:
Blocking SEMA4D via pepinemab would **reverse myeloid suppression** and **enhance** ICI **efficacy** in **metastatic melanoma**

Neoadjuvant biomarker trial

neoadjuvant pepinemab in combination with ipilimumab and/or nivolumab
in patients with resectable metastatic melanoma (NCT03769155)

Investigator Sponsored Neoadjuvant Biomarker Trial at Emory University led by
Michael Lowe, MD, Chrystal Paulos, PhD, and Greg Lesinski, PhD

Inclusion criteria

Biopsy accessible surgically resectable stage IIIB, IIIC, IIID disease

No prior immunotherapy for melanoma

1	2	3	4
Pre-treatment Day 1	**2 preoperative doses** Day 1 & 21 n=8 per treatment cohort (38 total) Open-label, Sequential enrollment	**Surgery** Day 35-49	**Follow-up endpoints**
Tumor needle biopsy **Blood draw**	**pepinemab** 20mg/kg **nivolumab** 480mg **ipilimumab** 1mg/kg **pepinemab** 20mg/kg **nivolumab** 480mg **pepinemab** 20mg/kg **ipilimumab** 1mg/kg **nivolumab** 480mg Surgery only (n=6) **Blood draw (2 wks)**	**Tumor-involved lymph nodes collected during surgical resection** **Blood draw**	**Outcome Measures** **Primary** Multi-omic profiling of resected tumor and peripheral blood to evaluate treatment-induced immune response **Secondary** Safety / tolerability Major pathologic response (mPR) Recurrence-free survival (RFS)

Overcoming study limitation by adding synthetic cohort

nivolumab 1mg/kg
ipilimumab 3mg/kg

Tissue samples from patients treated with nivo + ipi were **provided by Jennifer Wargo, MD, MD Anderson (NCT02519322)** and used as a"synthetic control" for the Emory trial cohorts

FFPE lymph node resections were analyzed together with Emory cohorts for comparative biomarker profiling

Multiomic Biomarker Analysis

Sample Processing

Blood

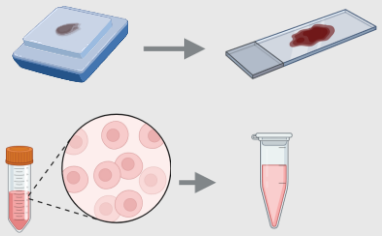
Peripheral blood timepoints

- Pre-treatment
- 2 weeks
- time of surgery

Resected LN Tumor

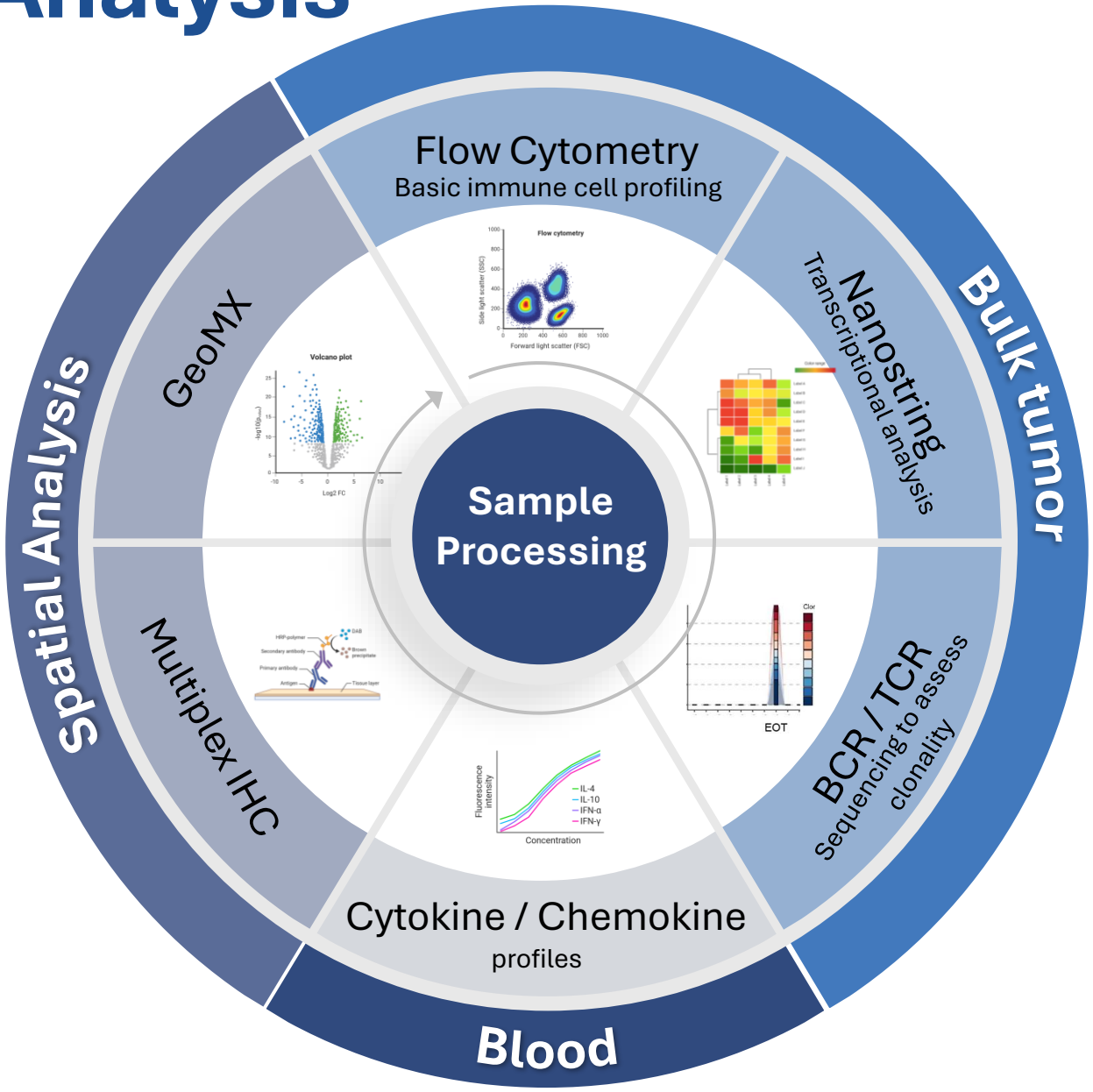
Pathologist assessed resected LNs to determine pathologic response

Processed for FFPE Block



Dissociated for Flow cytometry

*From each patient, one representative LN was selected for biomarker profiling based on pathology review



Ruffin et al. Manuscript in preparation

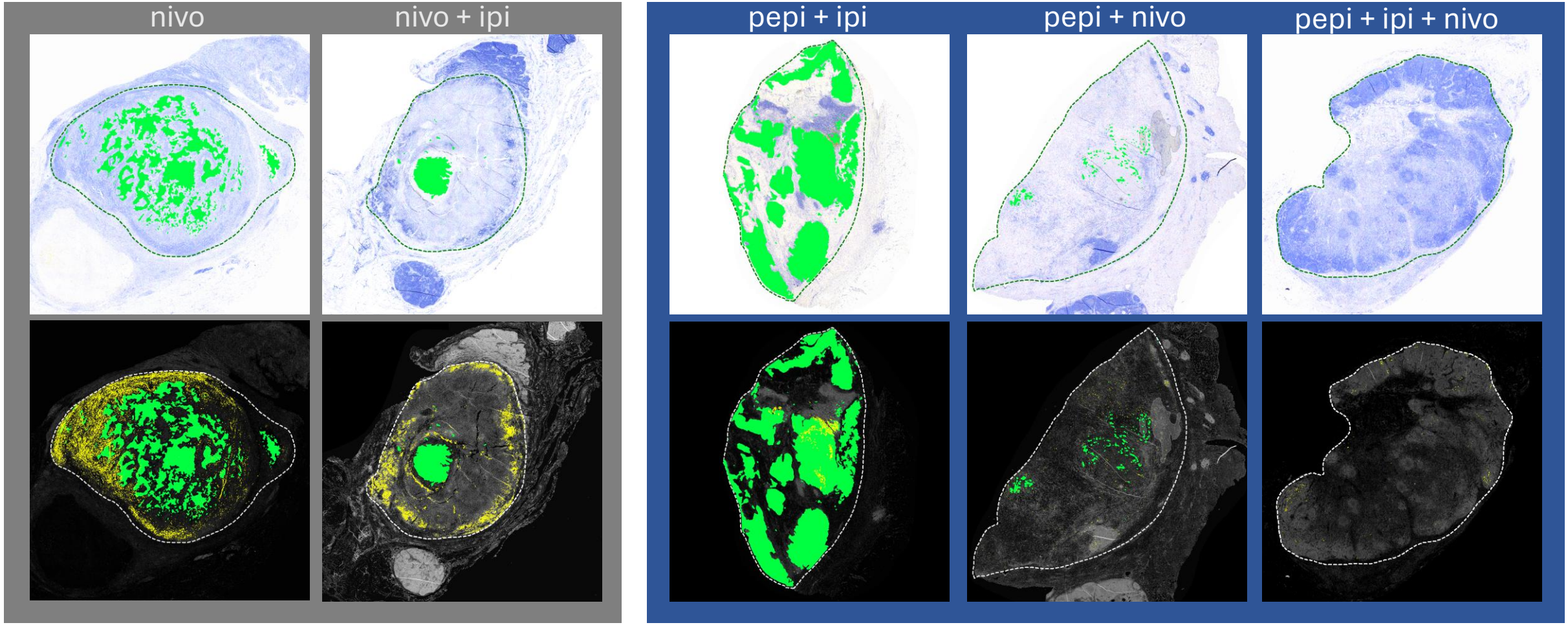
SEMA4D at periphery has been neutralized

Control arms

SEMA4D-positive cells clustering at periphery of tumor bed

Pepi containing arms

SEMA4D cells dispersed throughout tissue



Tumor cells
SEMA4D+ cells
TME

nivolumab = nivo
ipilimumab = ipi
pepinemab = pepi

- Classified representative images from resected on-treatment LN in metastatic melanoma
- TME determined by pathologist review and defined as “not normal LN architecture”

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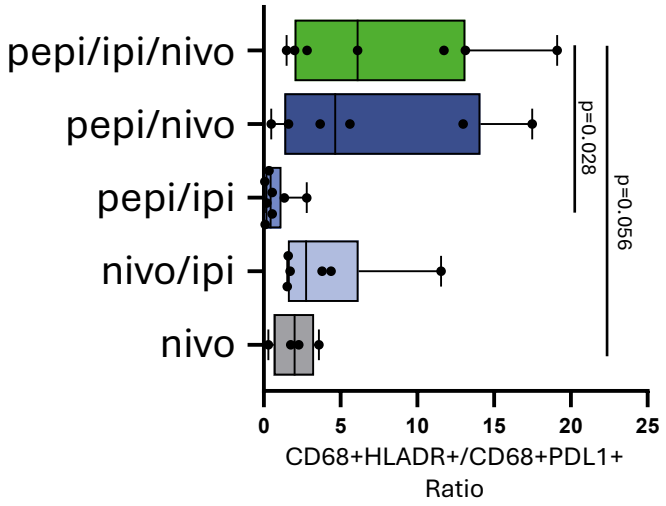
Neutralizing SEMA4D shifts the myeloid landscape from suppressive to immune-activating

Ratio

Activated APC

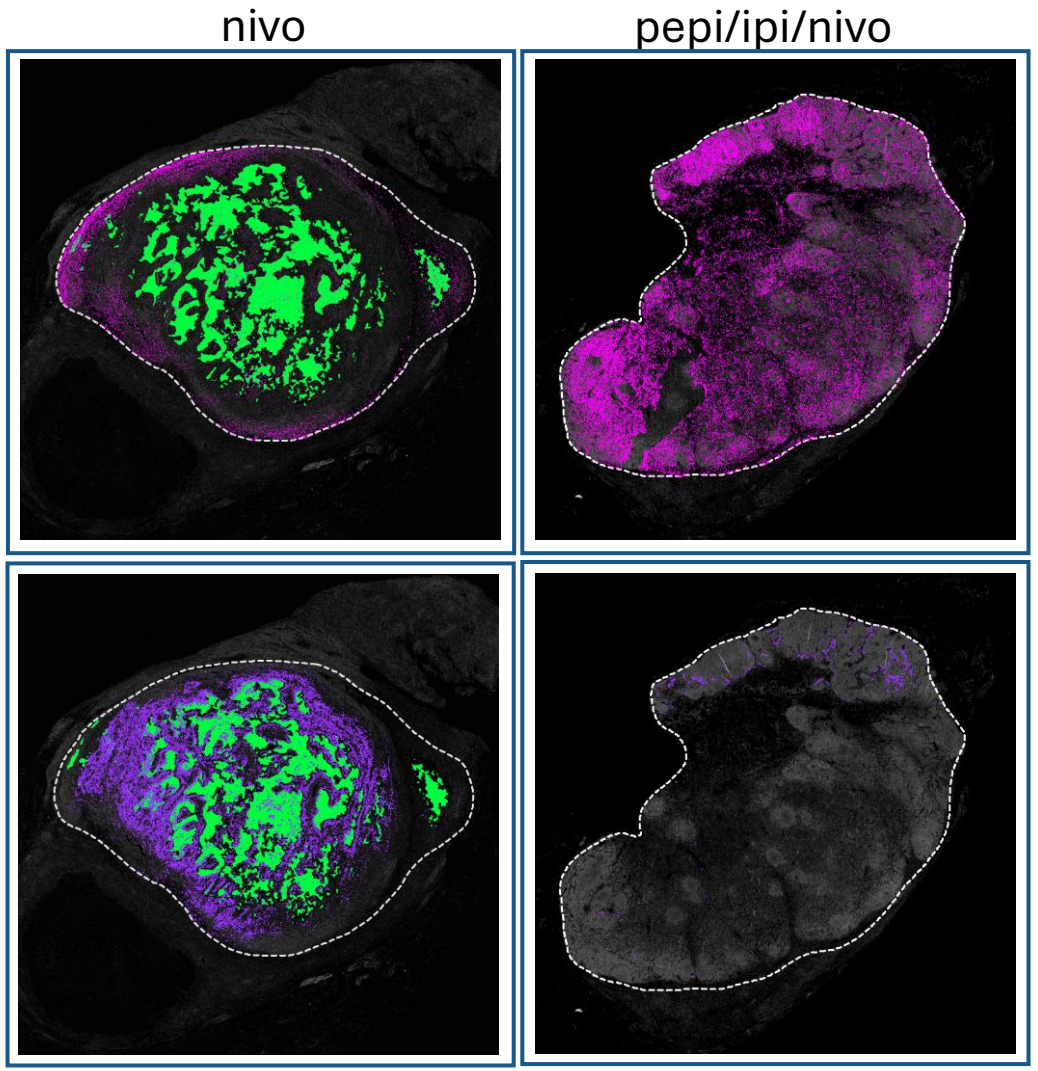
Suppressive Myeloid

pepi+ipi+nivo, had a higher ratio of activated antigen-presenting cells (HLA-DRhi) to suppressive myeloid cells in TME compared to ICI alone



Activated APC with pepi treatment:

- penetrate deep within TME
- Not restricted to periphery



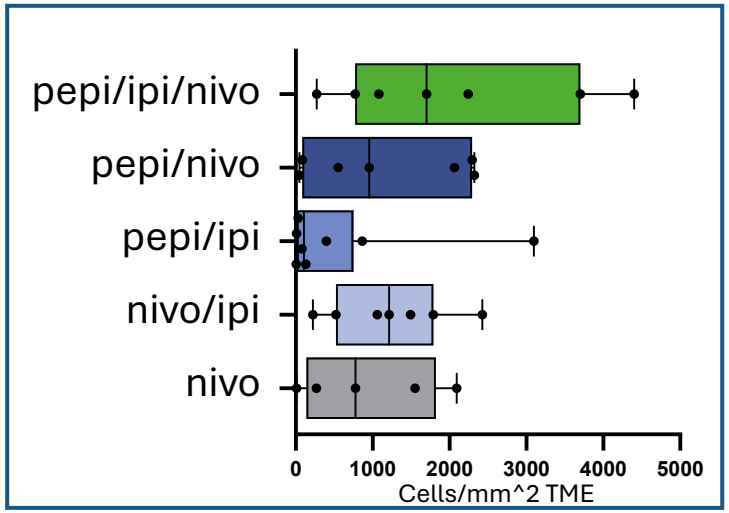
Releasing myeloid suppression alters the immune landscape

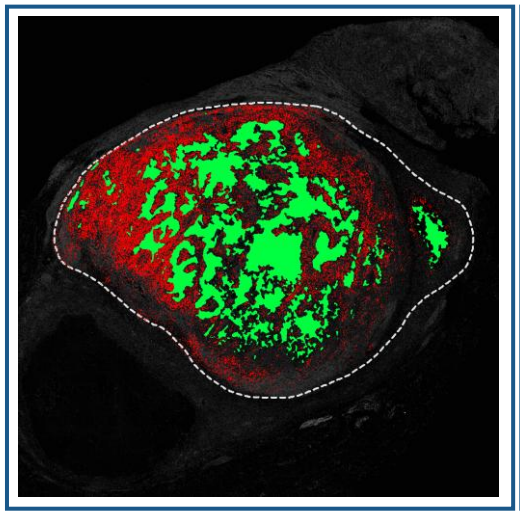
Increase in T cell infiltration

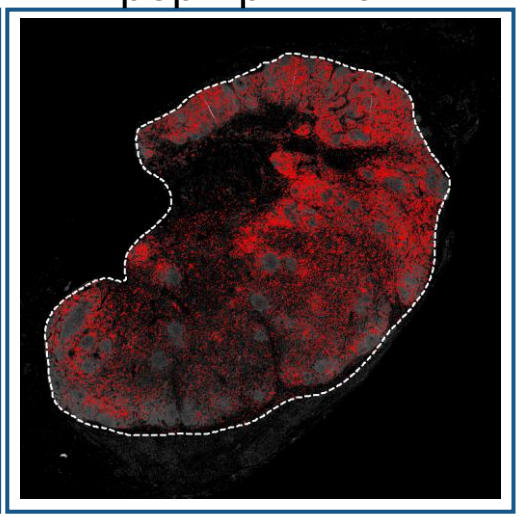
Restricted to tumor periphery
nivo

No longer restricted to tumor periphery
pepi/ipi/nivo

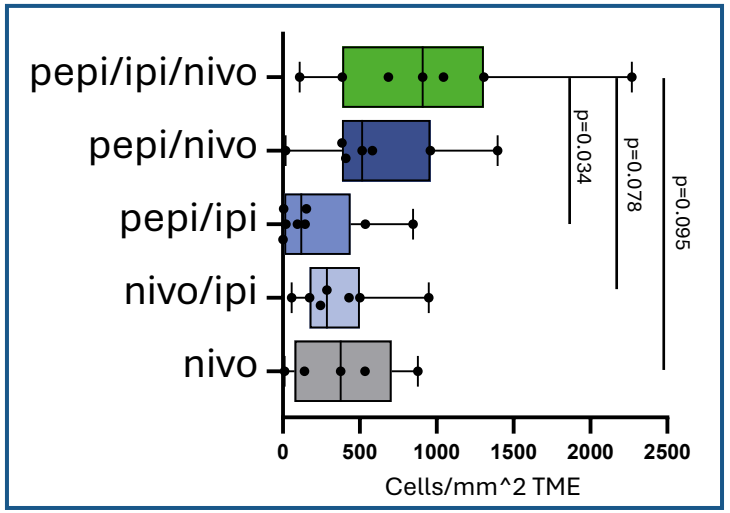
CD8 T cells

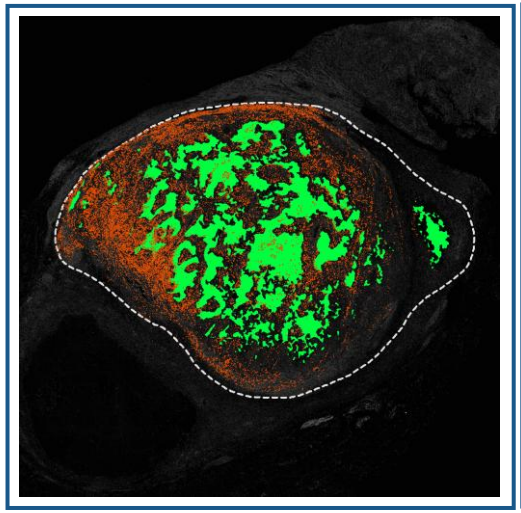


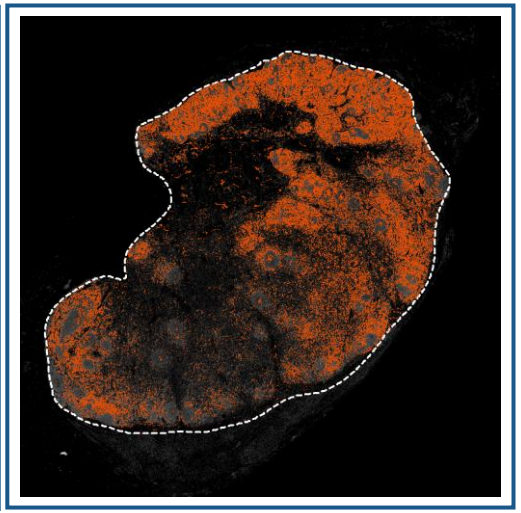




CD4 T cells





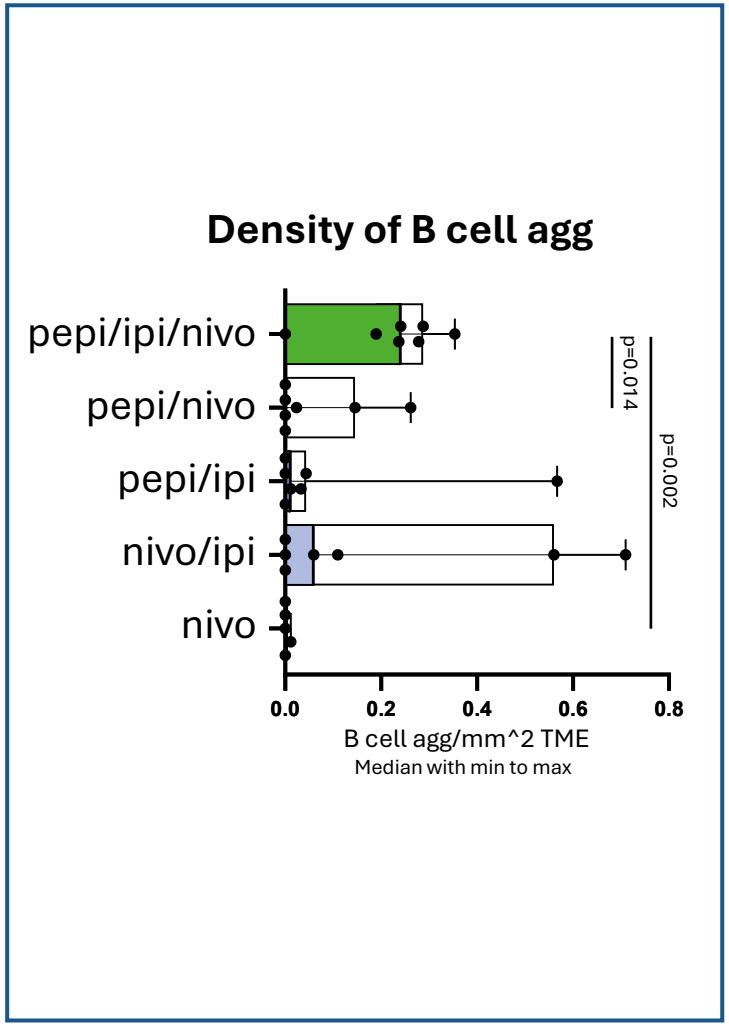


Tumor cells
TME

CD8+ T cells
CD4+ T cells

Increased infiltration of B cell aggregates

B cell Aggregates
(≥20 CD20 cells per cluster)

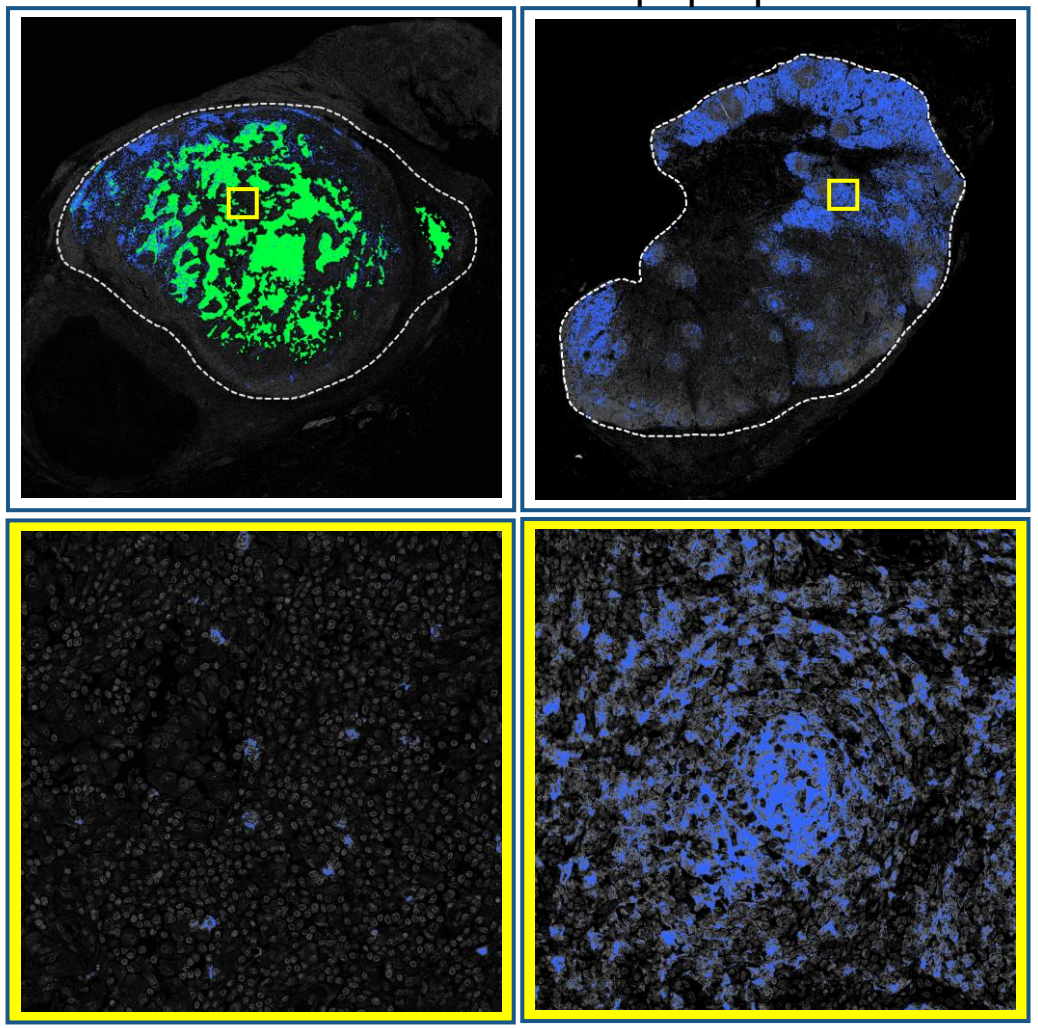


Diffusely distributed

nivo

B cell clustering

pepi/ipi/nivo



Tumor cells

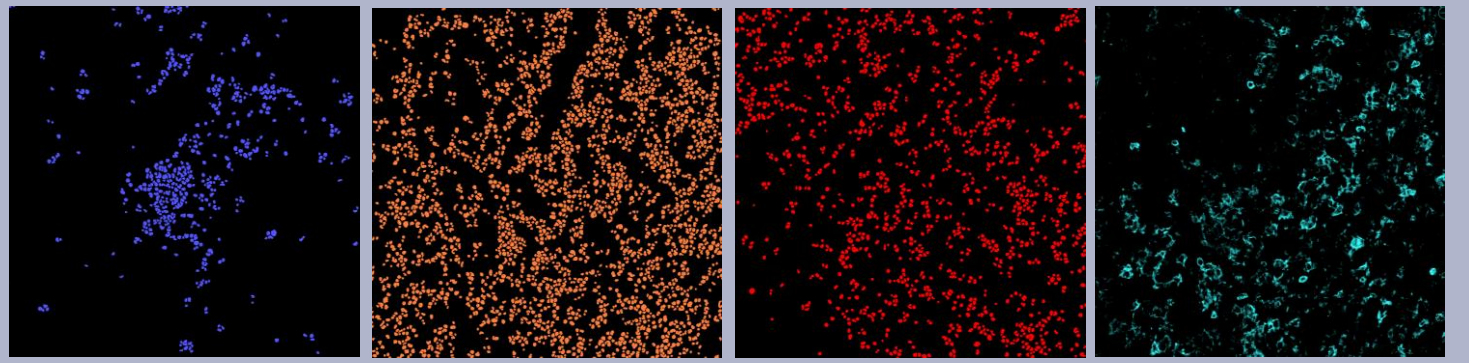
TME

CD20+ B cells

Defining mature vs immature

lymphoid aggregates (LAs) “tertiary lymphoid structures”

Immature lymphoid aggregates (iLA)



CD20 agg
≥20 B cells clustering

CD4 T cells / Tfh
CD4+FP3-

CD8
T cells

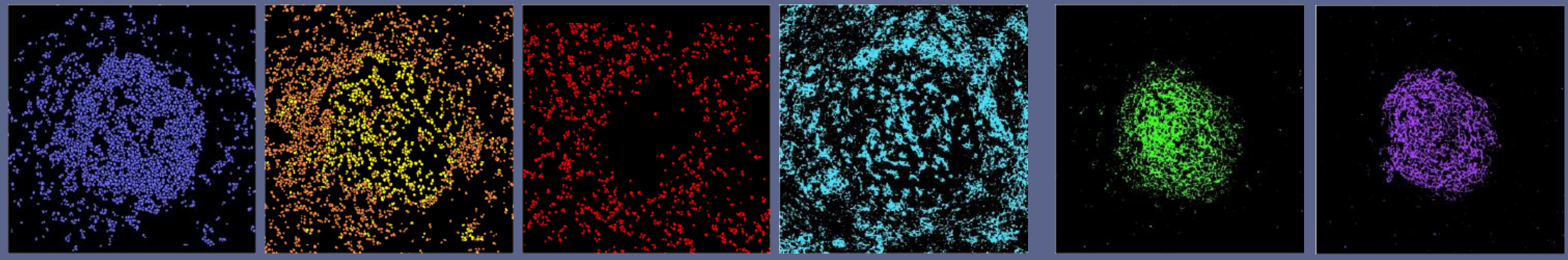
DC
CD11c+

Immature – varying states of organization

Defining mature vs immature

lymphoid aggregates (LAs) “tertiary lymphoid structures”

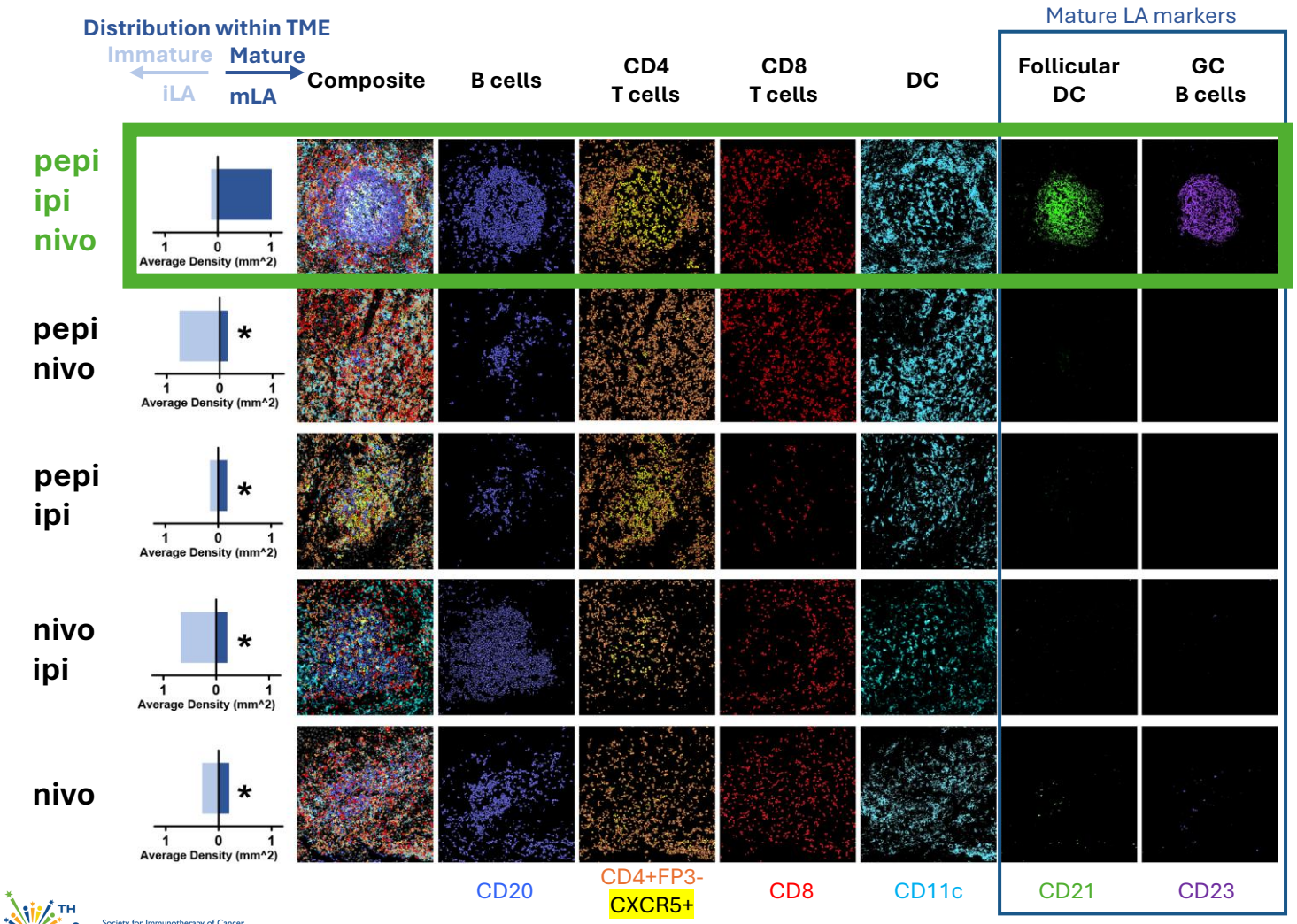
Mature lymphoid aggregates (mLA)



CD20 agg	CD4 T cells / Tfh	CD8	DC	Follicular DC	GC B cells
≥20 B cells clustering	CD4+FP3- CXCR5+	T cells	CD11c+	CD21+	CD23+

Mature – Distinct zones: B cell zone, T cell zone, and formation of germinal centers

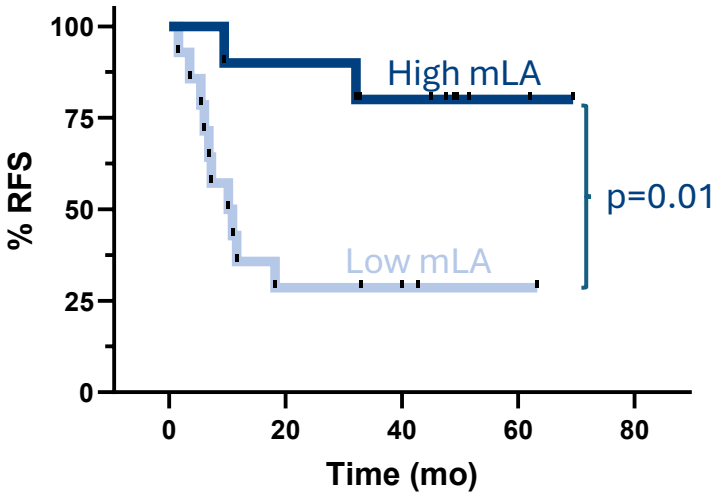
Increased maturity of lymphoid aggregates with pepinemab treatment



Representative LA from on-treatment patient LN resections

Increased abundance of mature LAs correlates with enhanced recurrence-free survival

regardless of the level of immature LA



Number at risk (number censored)

mLA high	10 (0)	9 (0)	7 (1)	2 (6)	0 (8)
mLA low	14 (0)	4 (0)	3 (1)	1 (3)	0 (4)
	0	20	40	60	80

Cutpoint analysis run in R to determine high vs low density cutoffs for the dataset.

This suggests that **mature lymphoid architecture** may be a key biomarker of durable response

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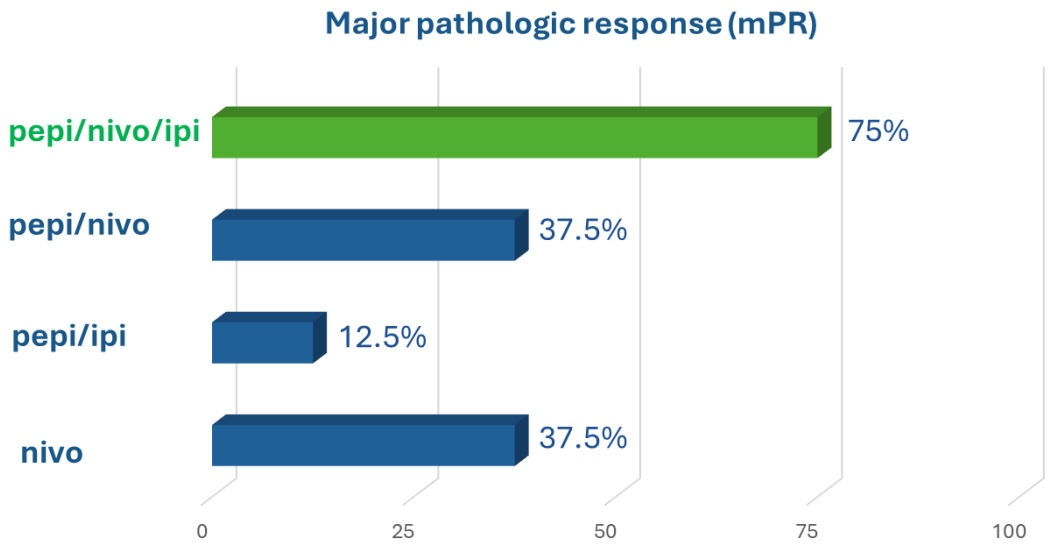
Secondary clinical outcomes

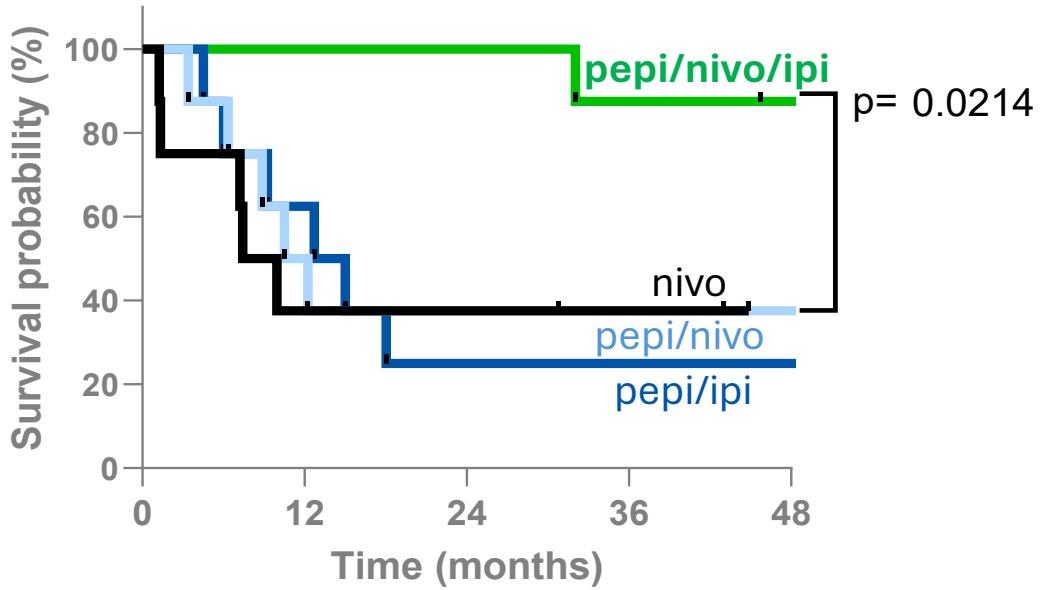
Combining pepinemab with nivolumab and ipilimumab enhances clinical efficacy in metastatic melanoma

Improved major pathologic response



n=8 per cohort

Prolonged recurrence-free survival



n=8 per cohort

Without additional toxicity beyond those expected from ICI

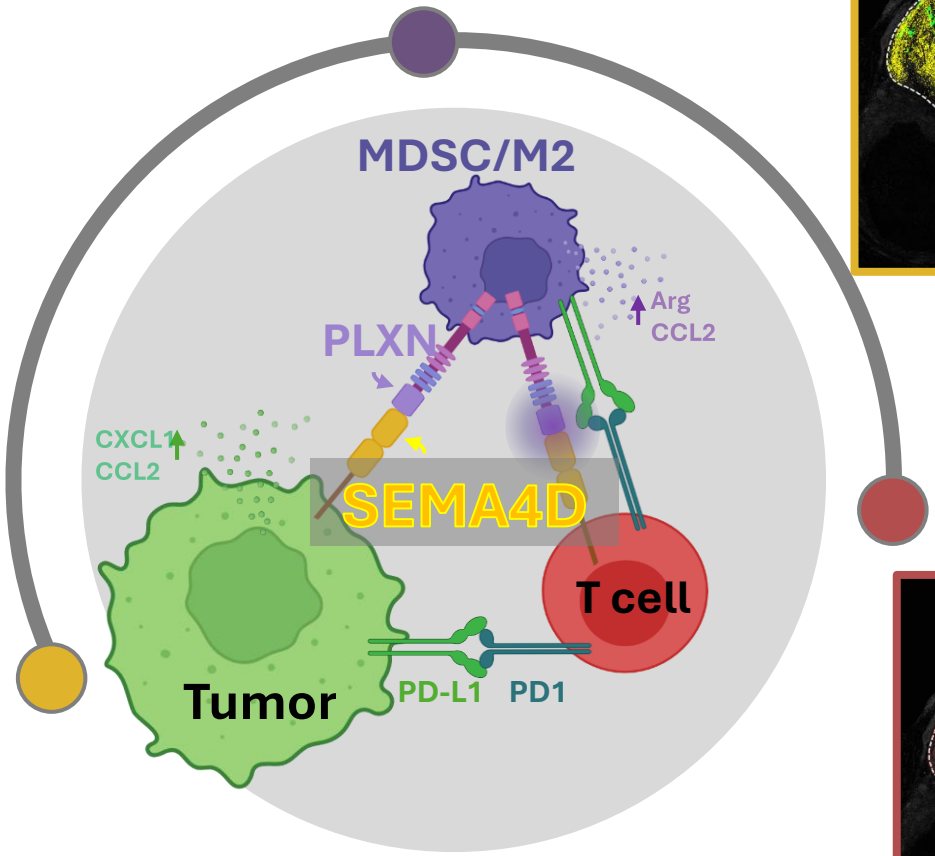
*no additional toxicity beyond those expected from ICI, and no patients experienced toxicity that required delay in surgery or discontinuation of Tx

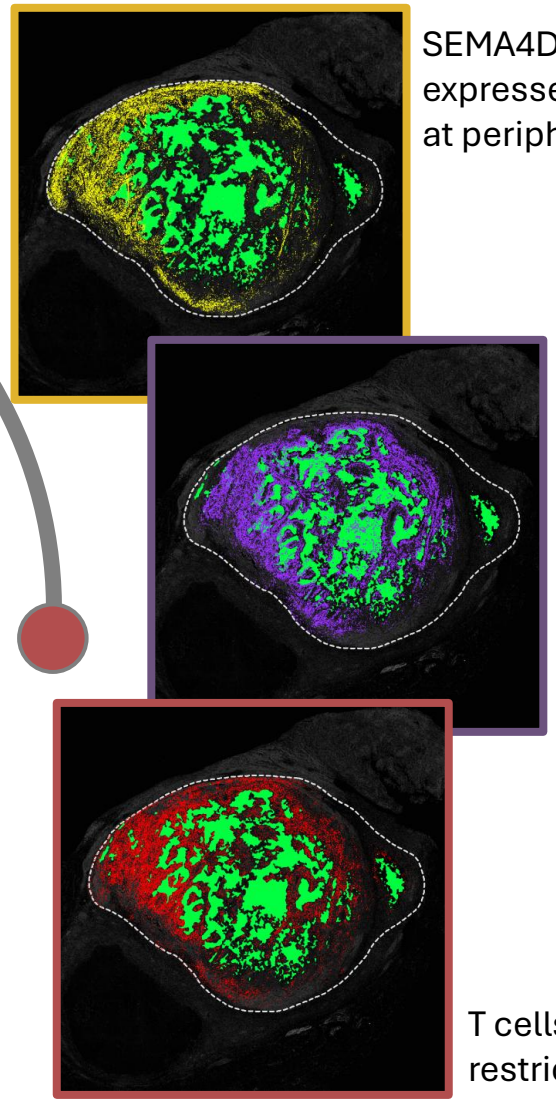
SEMA4D and Myeloid Suppression: A Critical Resistance Pathway

Neoadjuvant checkpoint therapy is increasingly becoming **standard of care** across multiple cancer types, including **metastatic melanoma**

Despite its promise, many patients still experience **resistance** or **disease progression** following treatment

SEMA4D expressed on **tumor and T cells** drives **myeloid suppression**, a key resistance mechanism of ICI





SEMA4D expressed at periphery

↑ Suppressive myeloid to activated APC ratio

T cells restricted

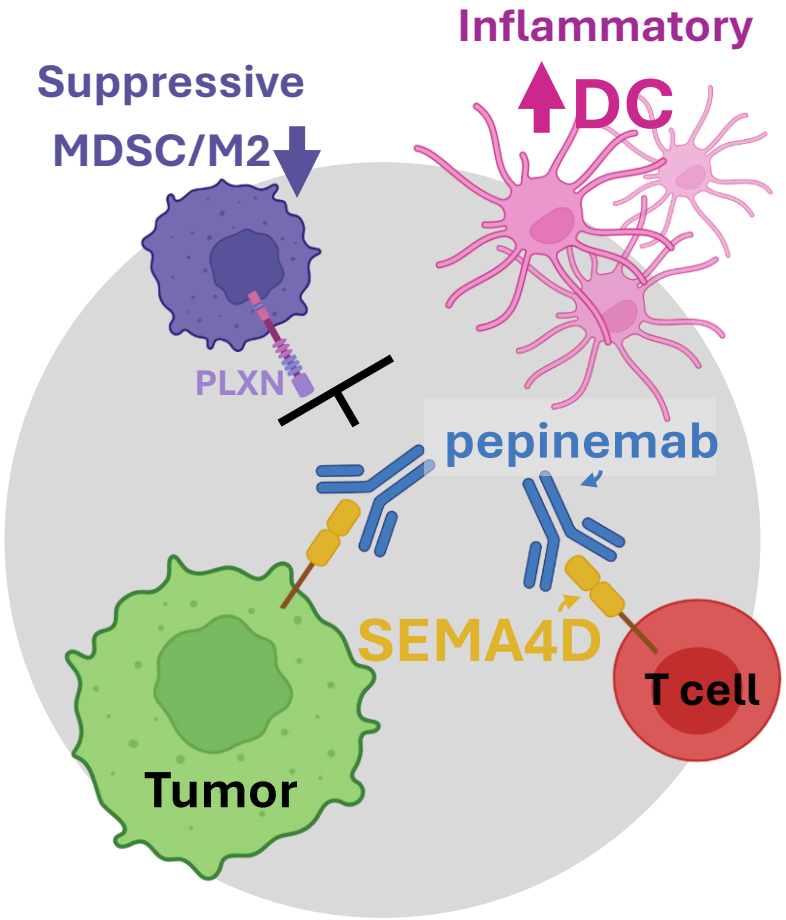
Sema4D blockade releases myeloid suppression

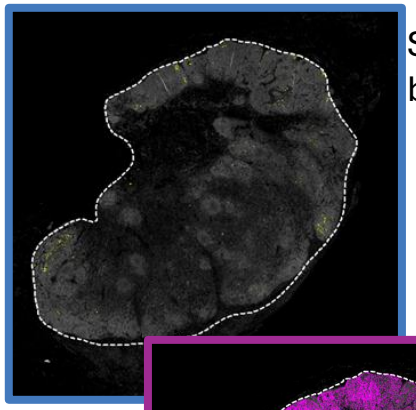
a novel immunotherapy to overcome resistance to ICI in the tumor microenvironment (TME)

Pepinemab, SEMA4D blocking antibody **releases myeloid suppression**

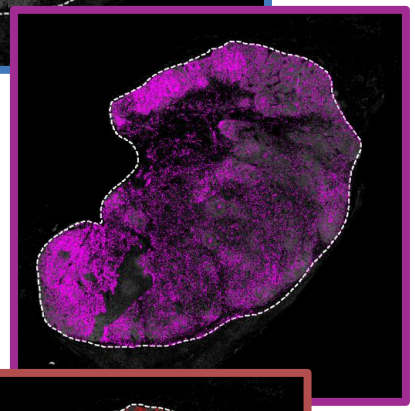
Shifts myeloid cell profile from **suppressive** to **immune activating**

Enhances **T cell function** and **infiltration** into the TME

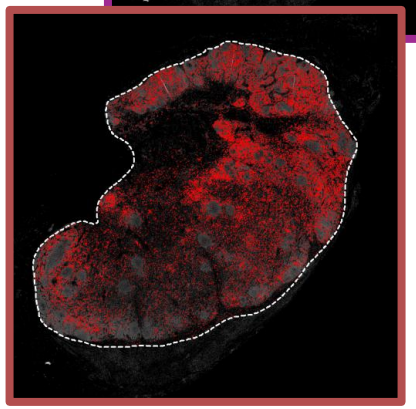




SEMA4D blocked



Activated APC

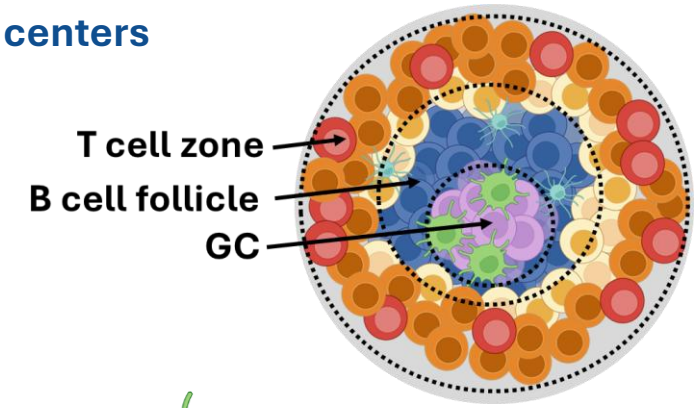


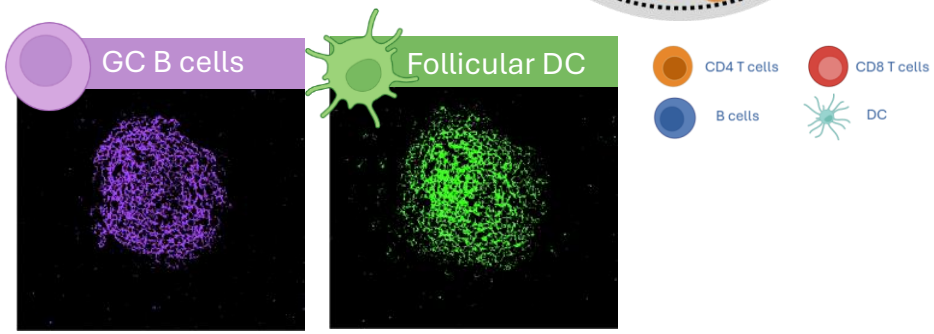
T cell penetration into TME

Sema4D blockade releases myeloid suppression

a novel immunotherapy to overcome resistance to ICI in the tumor microenvironment (TME)

- **SEMA4D blockade** also promotes an environment suitable for the formation of **mature lymphoid aggregates** containing **germinal centers**

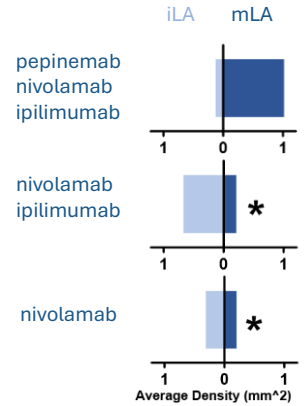




Representative mLA from pepi/nivo/ipi on-treatment patient LN resection

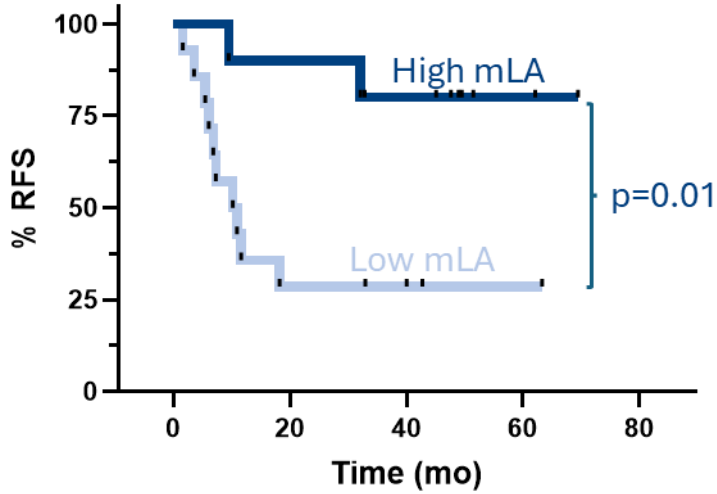
- These mature LA structures are associated with **organized immune responses** and were more prominent in the triple therapy cohort

Increased mLA in triple regimen including pepinemab



- Importantly, a **higher density of mature lymphoid aggregates** within the TME correlated with **prolonged recurrence-free survival**, suggesting a link between **lymphoid architecture** and **clinical benefit**

Recurrence-free survival



THANK YOU!

to our patients and their families

VACCINEX

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POSTER #22

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Saturday, Nov. 8, 2025

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