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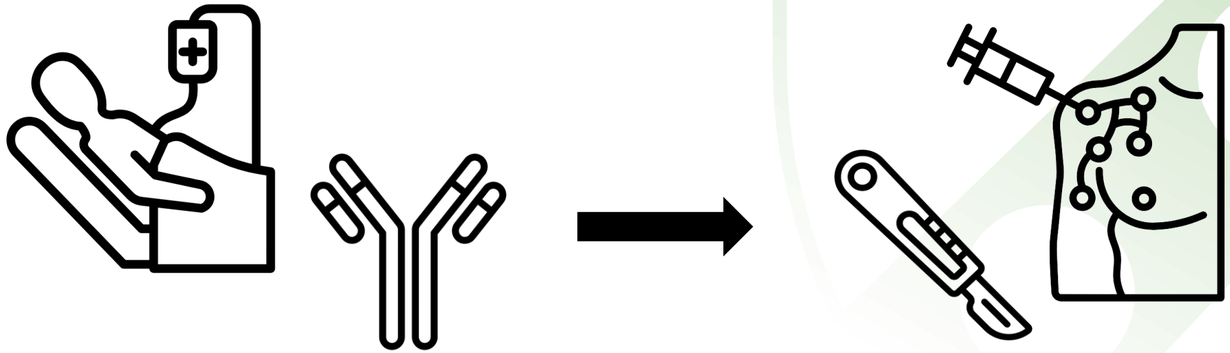
SOCIETY OF SURGICAL ONCOLOGY 2026

Neoadjuvant-adjuvant Pembrolizumab in Stage IIB/C Melanoma: Updated Clinical Outcomes and Translational Data from Phase II Trial NCT03757689



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Disclosure

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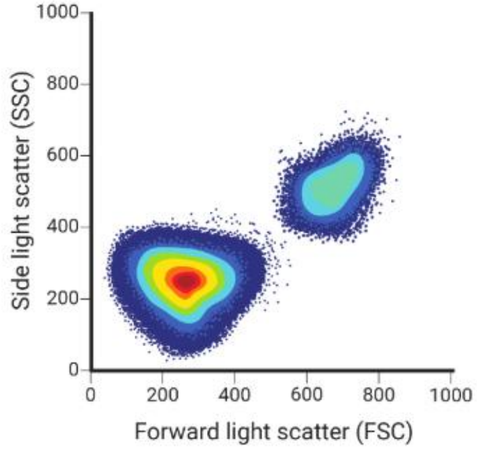
- Tara Mitchell – received honoraria for scientific advisory board participation from Bristol Myers Squibb, Merck, and Tempus

Overview

1. **Updated Clinical Outcomes**
   - SLN positivity rate
   - Survival outcomes

- **2. Translational Correlate Data**
  - Analysis of systemic circulation immune cells
  - Identification and clinical correlation of melanoma-specific CD8 T cells



Flow cytometry graph

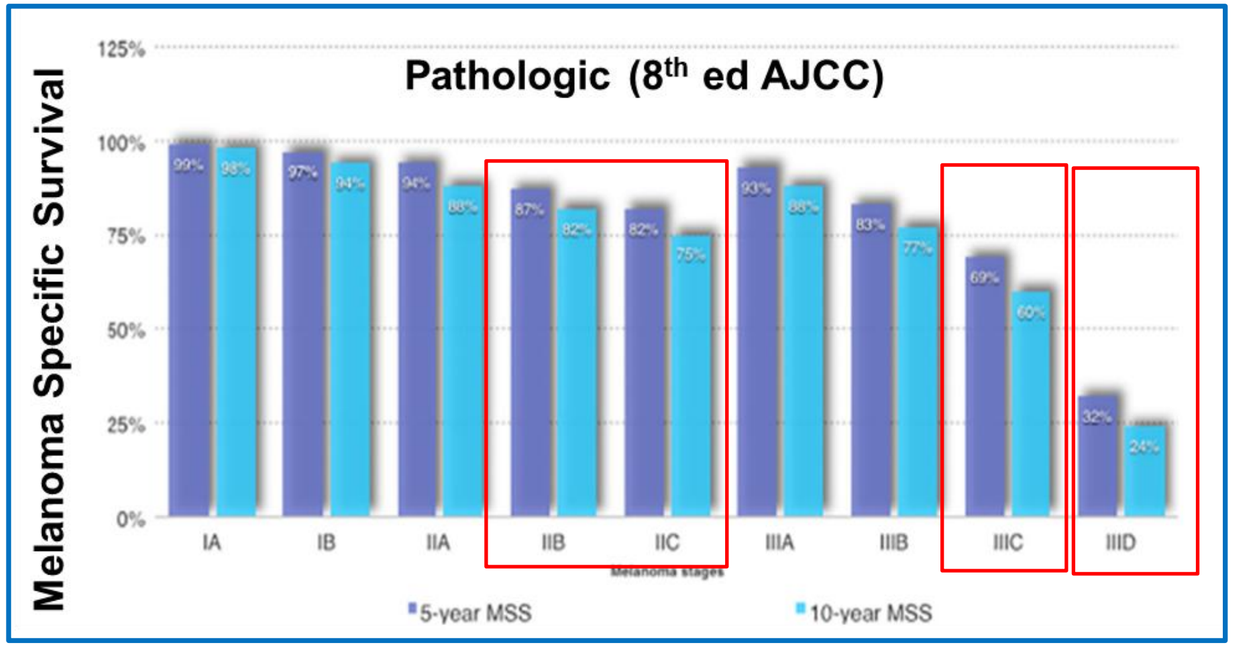
Background

- **Neoadjuvant immune checkpoint blockade improves EFS over adjuvant ICB for resectable advanced melanoma**

- **Stage IIB/C melanoma represents a high-risk patient population and ~ 1/3rd of patients with clinical Stage IIB/C will be upstaged to Stage IIIC/D**

- **Adjuvant anti-PD1 therapy improves RFS in pathologic Stage IIB/C melanoma with 2 yr RFS and DMFS rates of 81% and 88% (pembrolizumab)**

(Luke et al. *Eur J Cancer 2025*; Long et al Lancet Oncology 2022; Kirkwood et al. *Nature Med* 2023)



Napolitano et al Cancer Treatment Rev 2018. Modified by: Gershenwald JE, et al. CA Cancer J Clin. 2017

Trial Scheme

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NCT03757689

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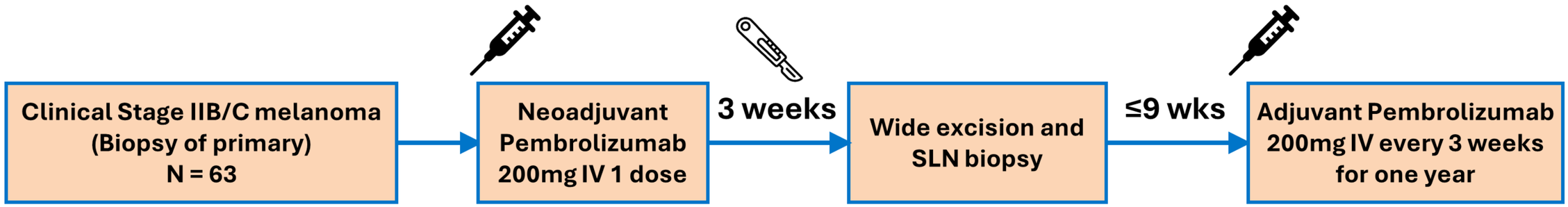
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

3 center open-label single arm phase II investigator-initiated neoadjuvant pembrolizumab clinical trial for Stage IIB/C melanoma (Accrual Feb 19, 2019-July 30, 2024)



Primary Endpoints:

- SLN positivity rate
- Safety and tolerability of PD-1 blockade in the peri- and post-operative setting

Secondary Endpoints:

- Recurrence-free survival and recurrence patterns
- Overall Survival

Primary Outcome – SLN Positivity Rate

Overall Cohort

	Trial Cohort % (No./total)	IIB/IIC	Historical Cohort %	% decrease	p-value*
SLN + rate (Bx)	27 (17/63)	33/30	32.1	16	0.384
SLN + rate (WLE)	27 (17/63)	29/34	33.1	18	0.334

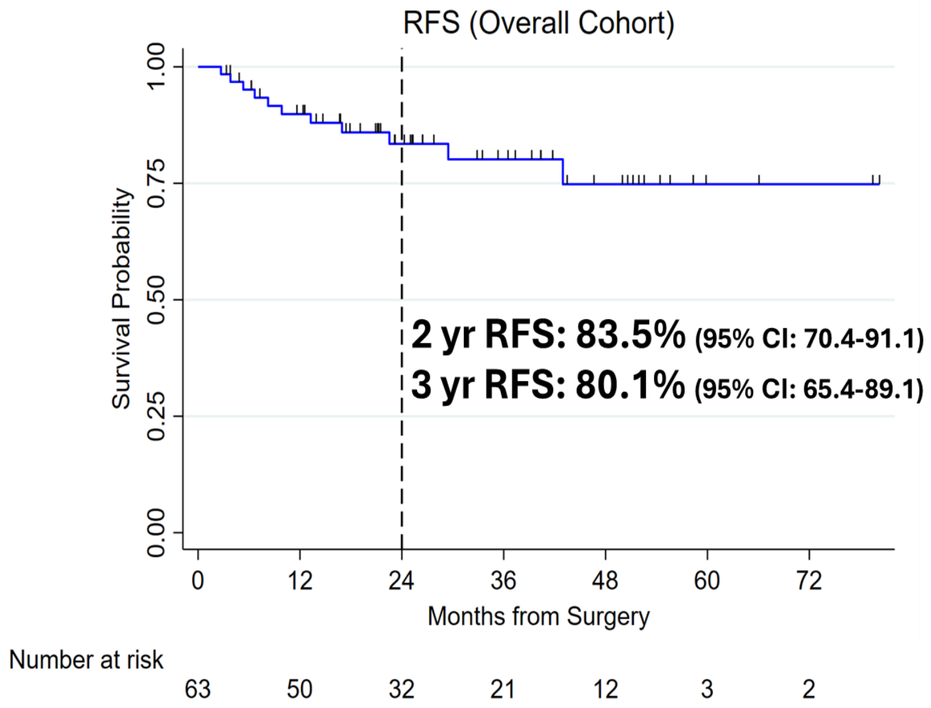
Stage IIC

	Trial Cohort % (No./total)	Historical Cohort %	% decrease	p-value*
SLN + rate (Bx)	16.7 (5/30)	40	58	0.009
SLN + rate (WLE)	23.5 (8/34)	40	41	0.0499

* 2-sided t-test

Secondary Outcomes – OS and RFS

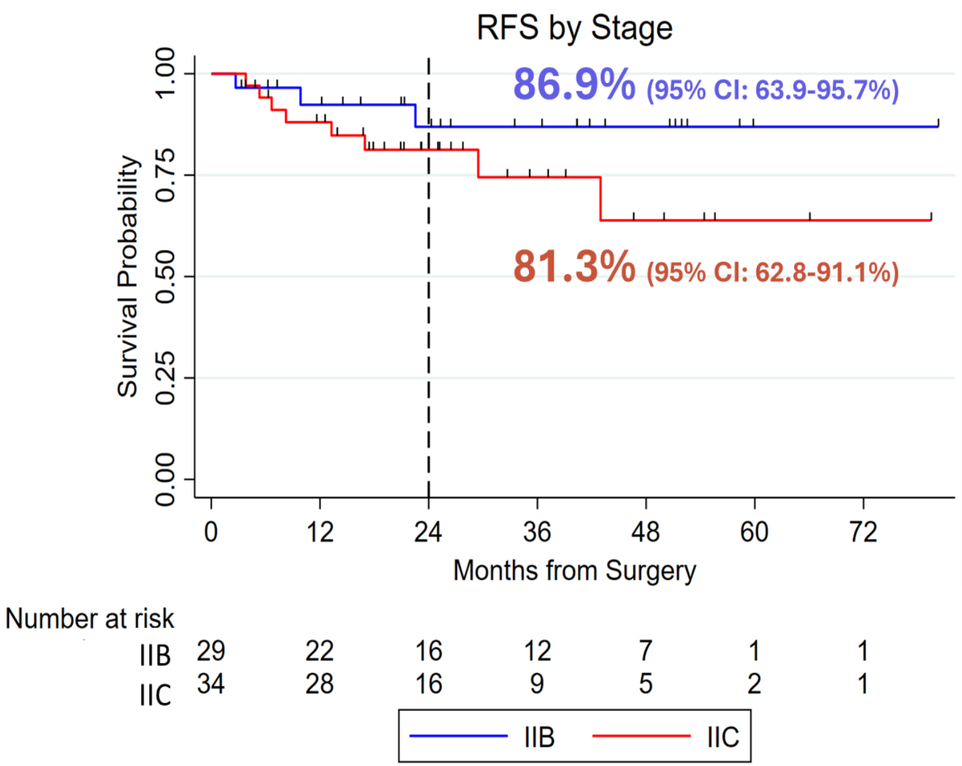
RFS Overall cohort



Median follow-up: 27.6 months

Median time to recurrence: 9.9 months

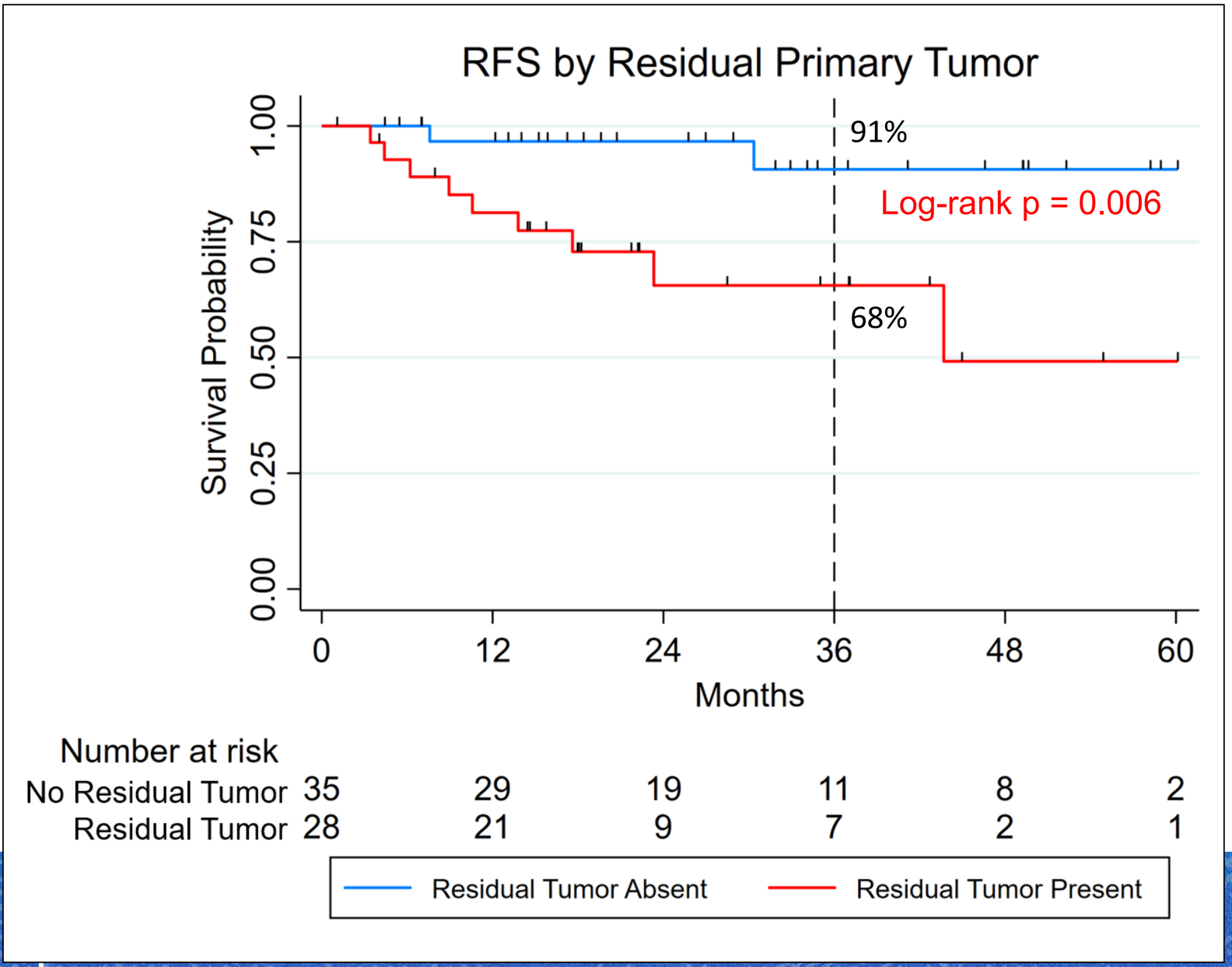
RFS by Stage grouping



Outcome	No. (%)
Recurrence	11/63 (17.4%)
Regional	4/63 (6.3%)
Distant	7/63 (11.1%)
Deaths	6 (9.5)
Deaths (disease related)	2 (3.2)
Deaths non-disease not treatment related	4 (6)

2 yr DMFS: 90.5% (95% 73.1-96.9%)

RFS stratified by Residual Primary Tumor on DOS



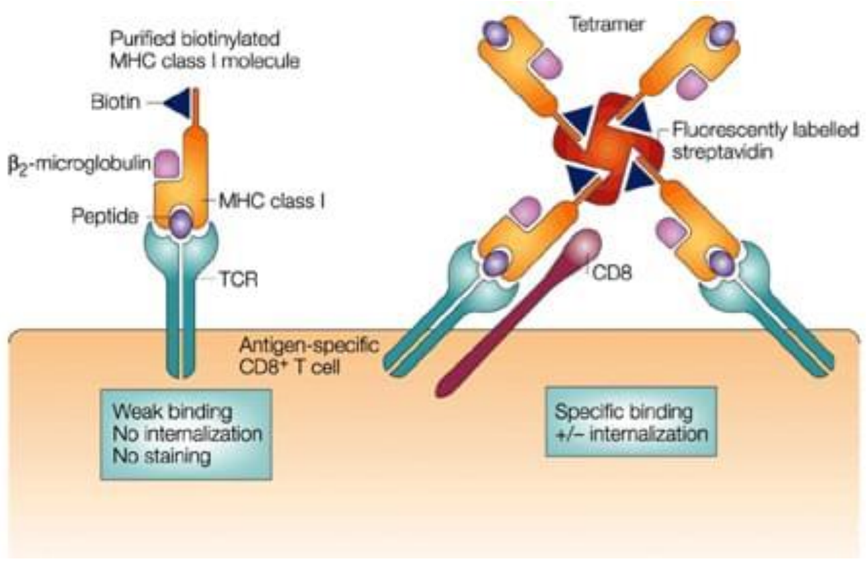
Residual Tumor: 28/63 (44%)
aHR: 6.37 (1.17 – 34.9, p = 0.033)

Translational Experimentation Aims

- **Aim 1** – characterization of immune cell subsets in systemic circulation
- **Aim 2** – correlate systemic and SLN findings with clinical outcomes to identify responders

We hypothesized that neoadjuvant anti-PD-1 therapy in stage IIB/IIC melanoma will lead to increased circulating levels of overall and melanoma-specific CD8 T cells.

Experimental Plan: spectral flow cytometry with combinatorial tetramers for melanoma specific antigens

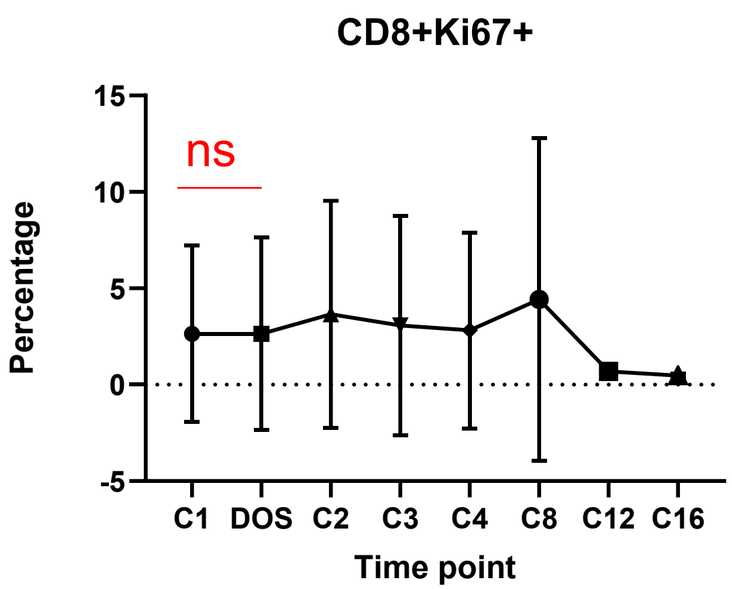


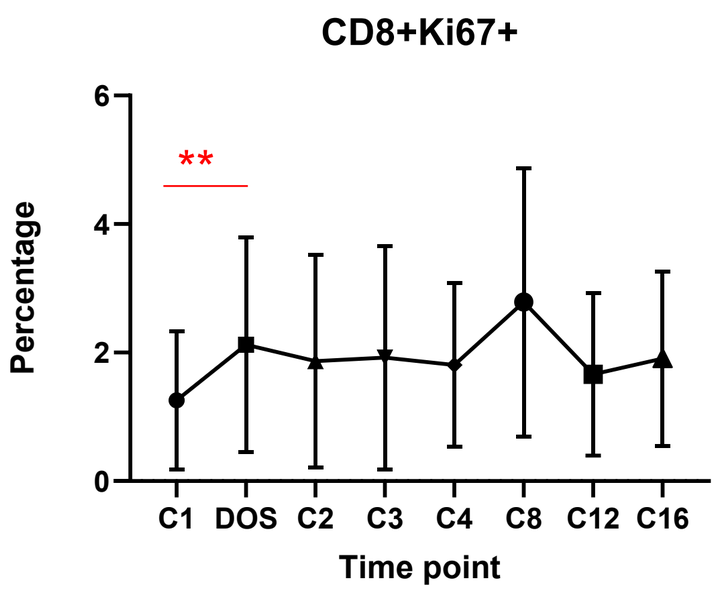
CD8 T Cell Proliferation Following Neoadjuvant Pembrolizumab

Stage IIB (n = 13)

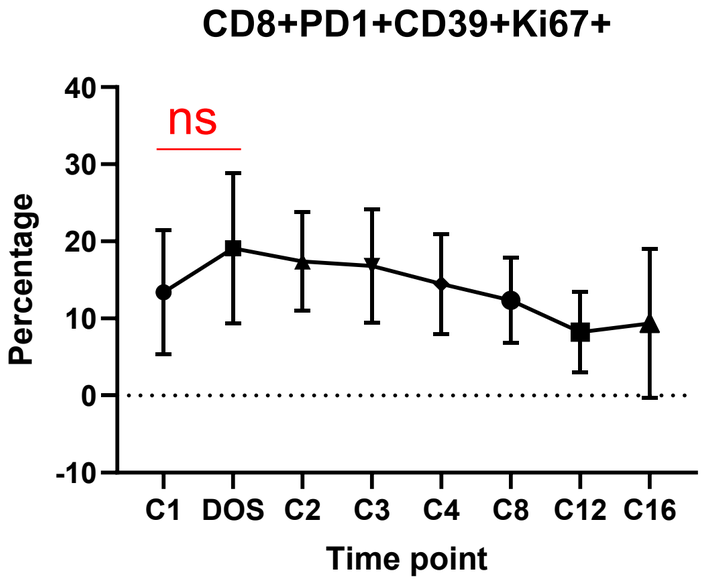
Stage IIC (n = 14)

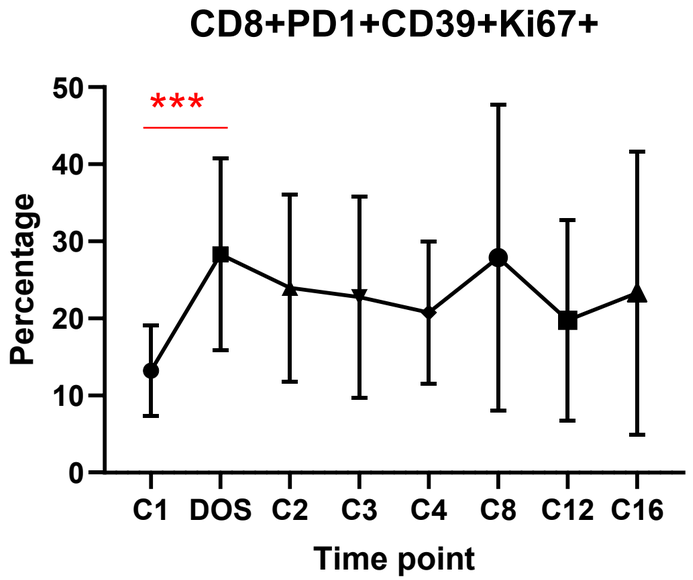
Ki67+





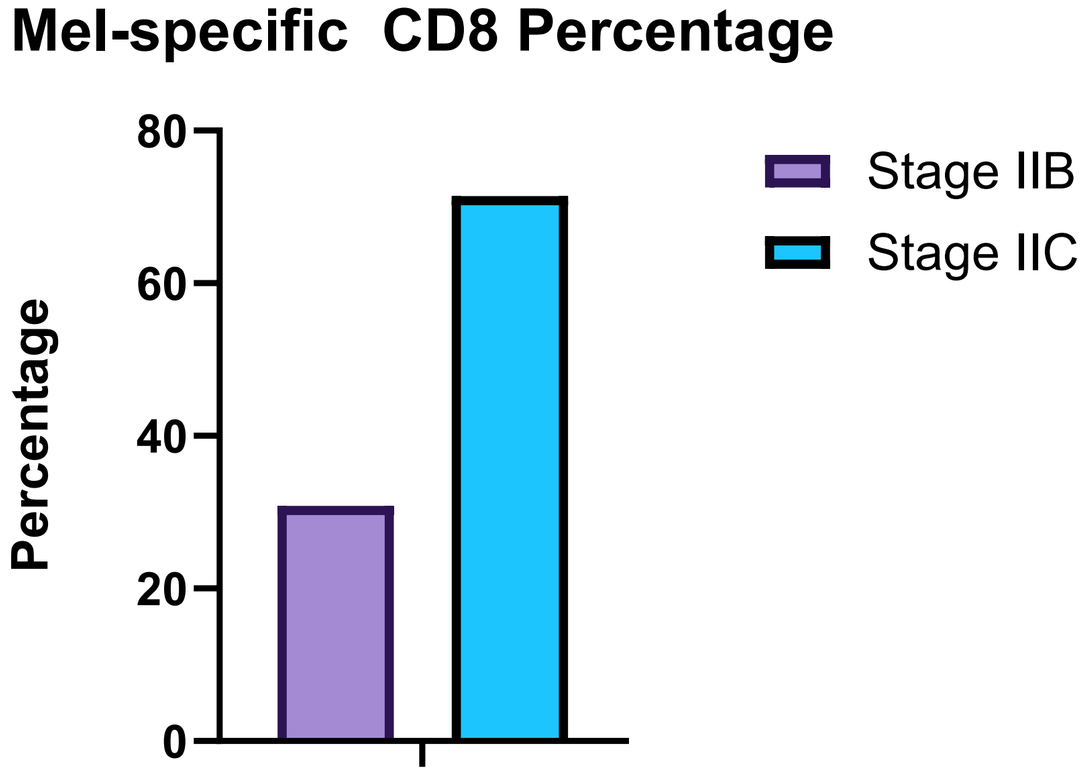
PD1+CD39+ (Exhausted)





Melanoma Specific CD8 T Cell Stage Distribution

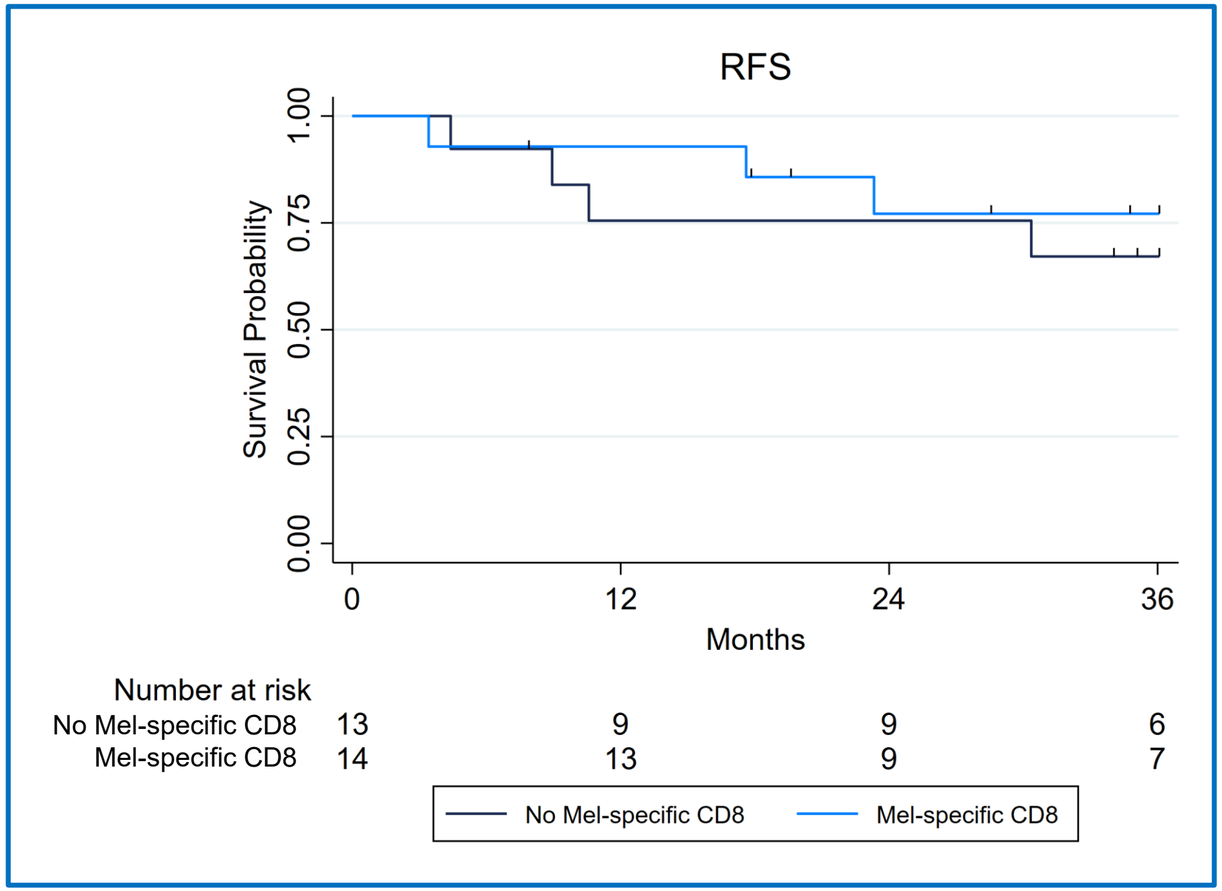
- **14/27 on C1/DOS (52%)**
  - IIB: 4/13 (31%)
  - IIC: 10/14 (71%)
- **Represented antigens**
  - MART-1
  - gp100
  - SOX10
  - Titin
  - Mage A3
  - AIM2



aOR (IIC vs. IIB): 5.9, 95% CI: 1.07 – 32.6, p = 0.041

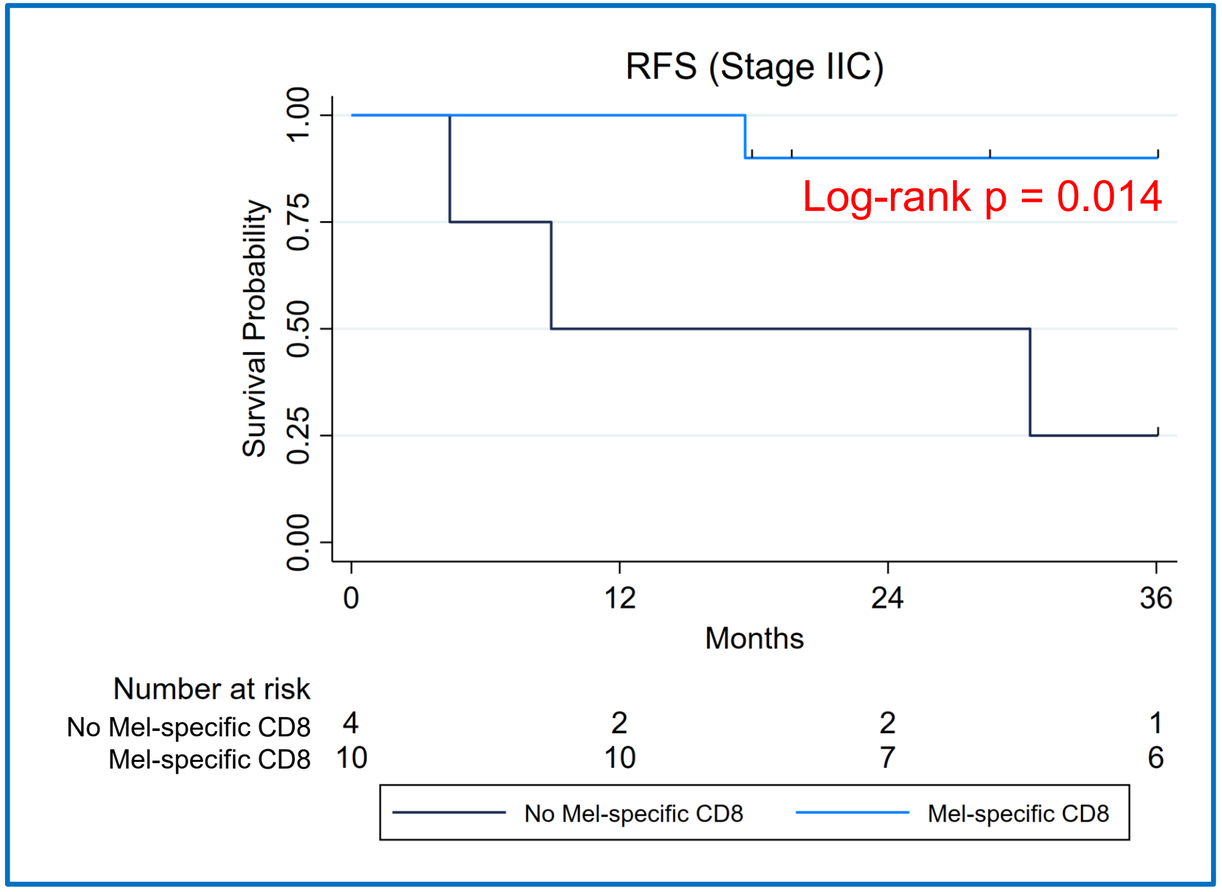
RFS – Melanoma Specific CD8 Cells

Overall Cohort (n = 27)



HR: 0.66, 95% CI: 0.15 – 2.97, p = 0.591

Stage IIC (n = 14)



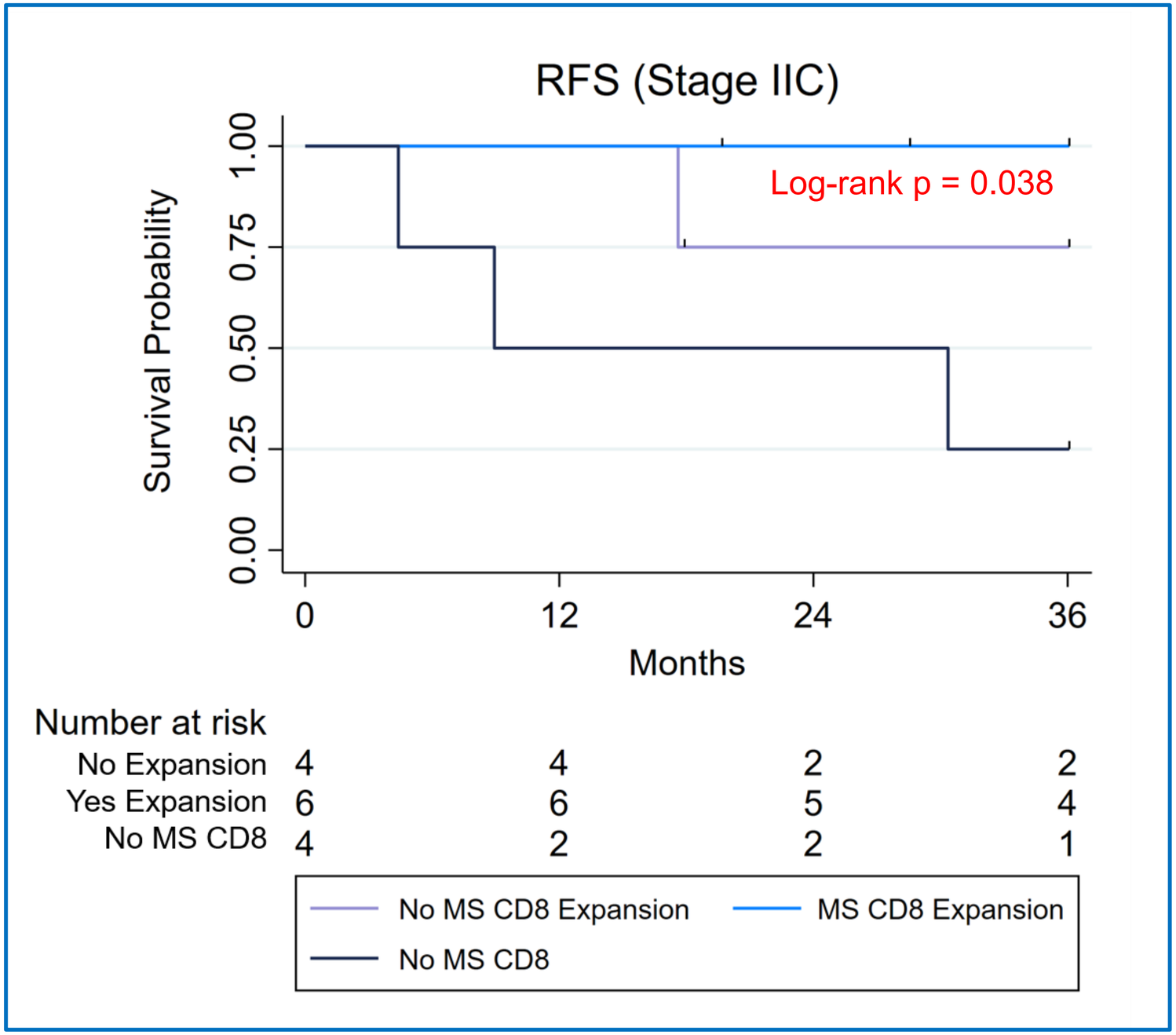
HR: 0.098, 95% CI: 0.01 – 0.96, p = 0.046

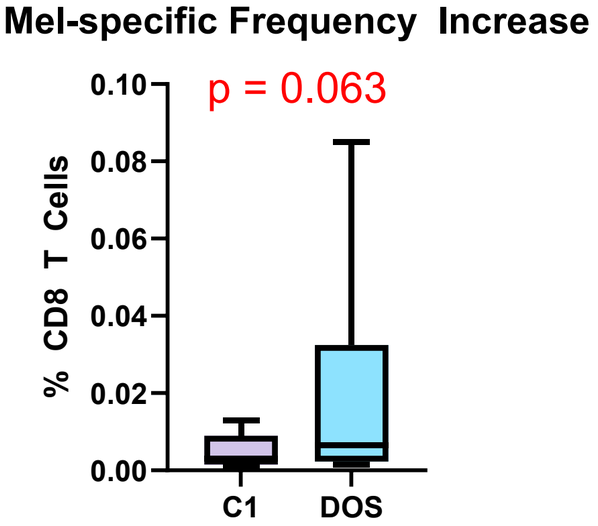
Median Breslow Thickness

No Mel-specific CD8: 7.1 mm

Mel-specific CD8: 8.1 mm

RFS – Stratified by Mel-specific CD8 T Cell Expansion





Median % C1: 0.0031
Median % DOS: 0.0065

Median Breslow Thickness

No DOS Expansion: 6.6 mm (4.9 – 19.9)
DOS Expansion: 8.25 mm (7 – 10.4)
No Mel-specific CD8: 7.1 mm (5.5 – 8.3)

Summary

1. **Single-dose neoadjuvant pembrolizumab in clinical is safe and exhibits favorable RFS compared to historical data**
   - SLN positivity rate was not significantly reduced in overall cohort but in subgroup of stage IIC patients
   - Presence of residual primary tumor is a potential pathologic biomarker
2. **Differential systemic circulation immune signatures between IIB and IIC**
   - Increased presence of melanoma specific CD8 T cells in IIC vs. IIB
     - Presence and expansion of melanoma specific CD8 T cells confer RFS advantage in IIC

Next Steps

1. Additional flow cytometric analysis to characterize immune cell subsets
2. Comprehensive bulk gene expression analysis of SLN
3. Xenium digital spatial transcriptomic analysis between SLN+ and SLN- patients

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