Sarcoma Immune Class (SIC) Data Review: TARPSWG STRASS3 Discussion

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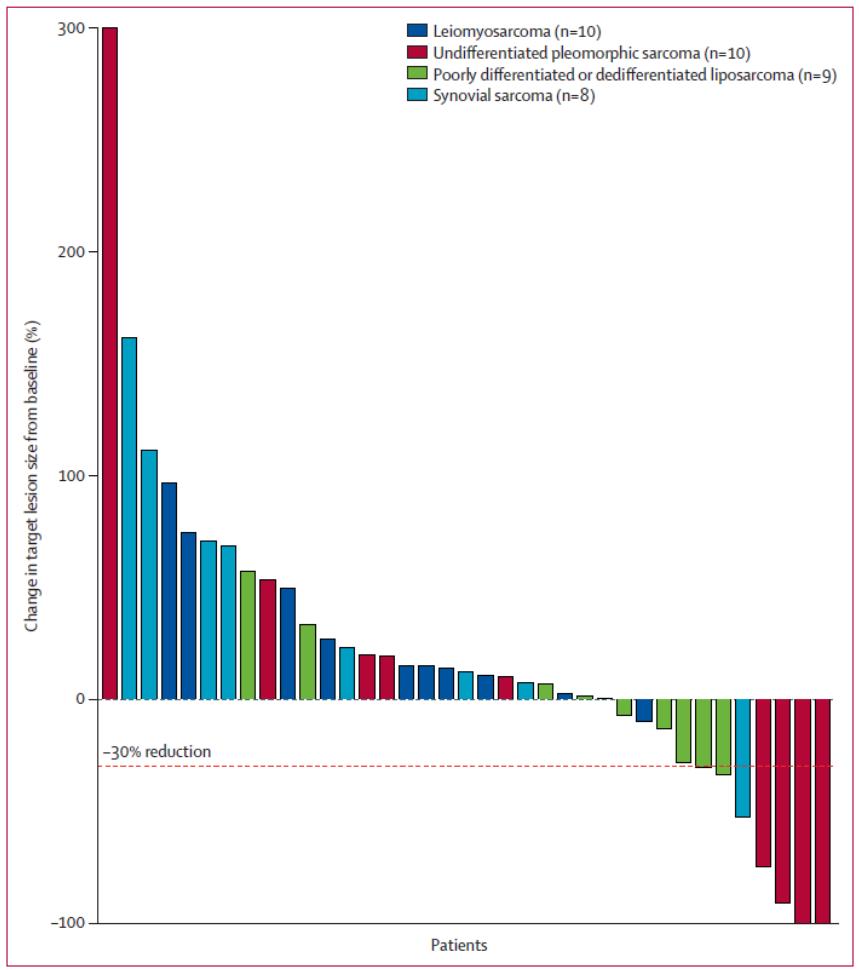
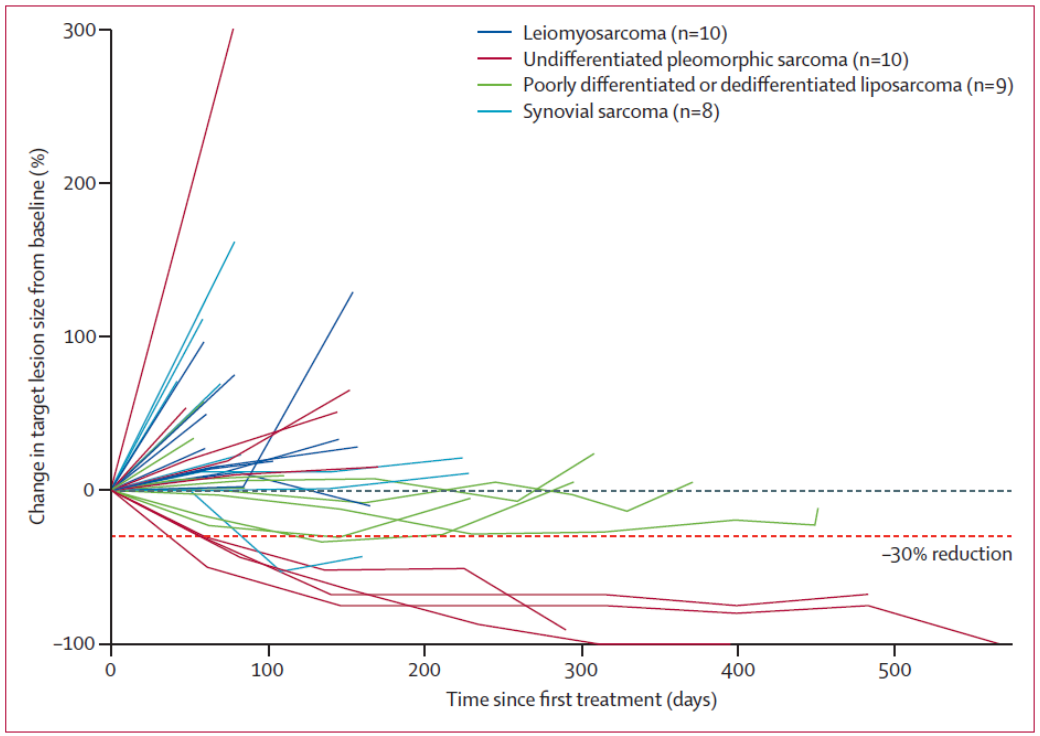
Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

Hussein A Tawbi, Melissa Burgess, Vanessa Bolejack, Brian A Van Tine, Scott M Schuetze, James Hu, Sandra D'Angelo, Steven Attia, Richard F Riedel, Dennis A Priebat, Sujana Movva, Lara E Davis, Scott H Okuno, Damon R Reed, John Crowley, Lisa H Butterfield, Ruth Salazar, Jaime Rodriguez-Canales, Alexander J Lazar, Ignacio I Wistuba, Laurence H Baker, Robert G Maki, Denise Reinke, Shreyaskumar Patel

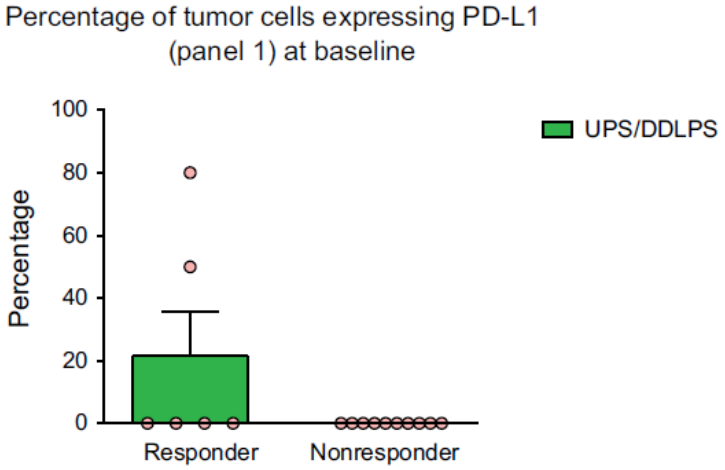


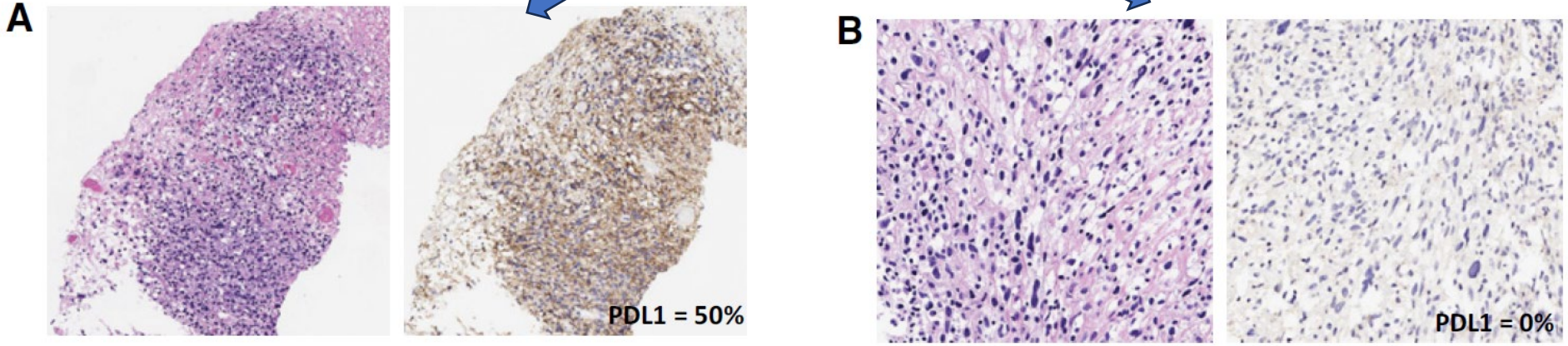


Lancet Oncol 2017; 18: 1493–1501

Correlative Analyses of the SARC028 Trial Reveal an Association Between Sarcoma-Associated Immune Infiltrate and Response to Pembrolizumab

- Multiplex IHC analysis of pre and post (8 week) treatment biopsies
- Focus on UPS/DDLPS



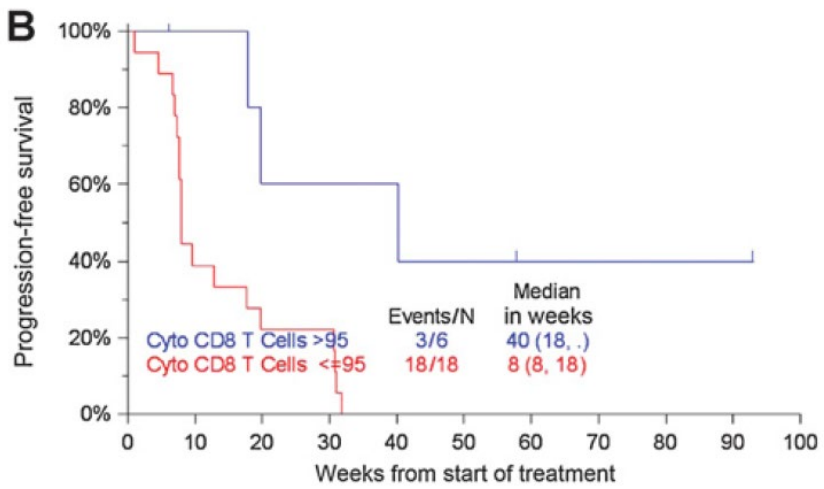


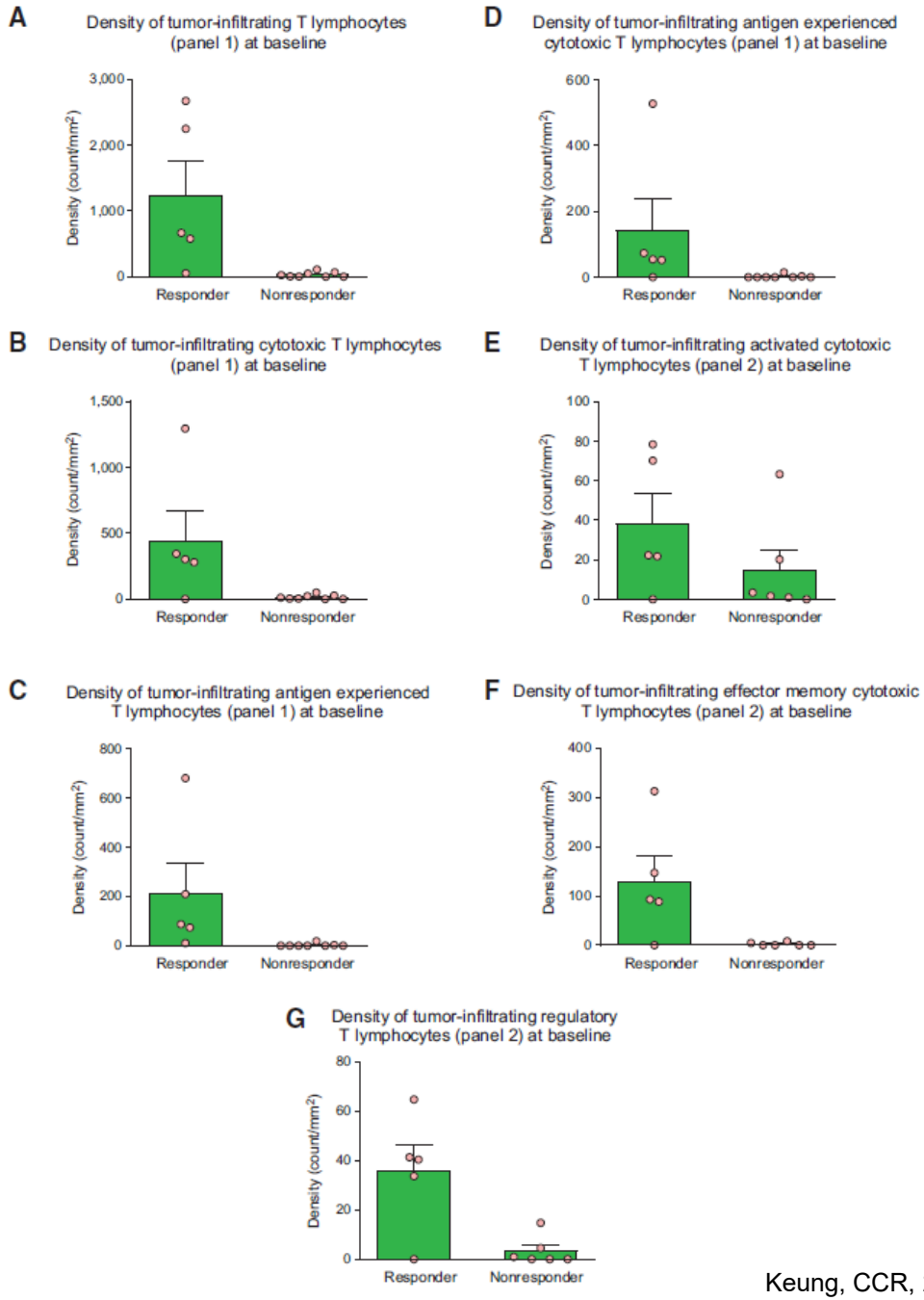
Keung, CCR, 2020

Correlative Analyses of the SARC028 Trial Reveal an Association Between Sarcoma-Associated Immune Infiltrate and Response to Pembrolizumab

Table 1. Definitions of immune cell phenotypes.

Immune cell type	Immune cell phenotype
Panel 1	
T lymphocytes	$(CD3^+\ CD8^+) + (CD3^+\ PD\text{-}1^+) + (CD3^+\ CD8^+\ PD\text{-}1^+) + (CD3^+)$
Cytotoxic T cells	$(CD3^+\ CD8^+) + (CD3^+\ CD8^+\ PD\text{-}1^+)$
T cells antigen-experienced	$(CD3^+\ PD\text{-}1^+) + (CD3^+\ CD8^+\ PD\text{-}1^+)$
Cytotoxic T cells antigen experienced	$CD3^+\ CD8^+\ PD\text{-}1^+$
Macrophages	$(CD68^+\ PD\text{-}L1^-) + (CD68^+\ PD\text{-}L1^+)$
Panel 2	
T lymphocytes	$(CD3^+\ CD8) + (CD3^+\ CD8^+\ GranzymeB^+) + (CD3^+\ CD8^+\ CD45RO^+) + (CD3^+\ FOXP3^+) + (CD3^+\ CD8^+\ FOXP3^+) + (CD3^+)$
Cytotoxic T cells activated	$CD3^+\ CD8^+\ GranzymeB^+$
Effector memory cytotoxic T cells	$CD3^+\ CD8^+\ CD45RO^+$
Regulatory T cells	$(CD3^+\ FOXP3^+) - (CD3^+\ CD8^+\ FOXP3^+)$



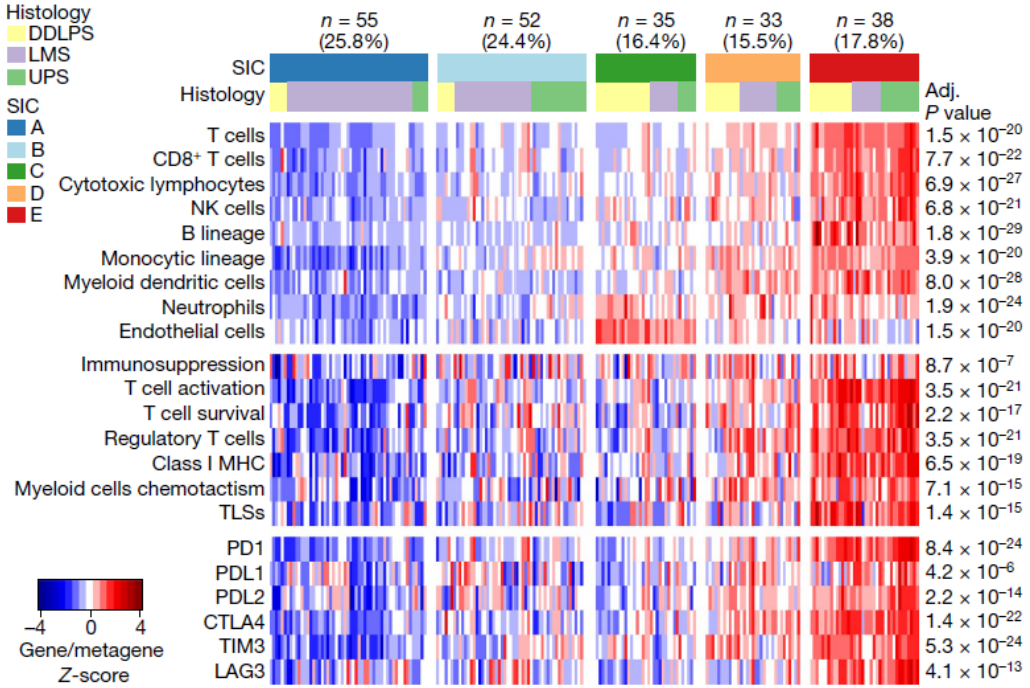


Keung, CCR, 2020

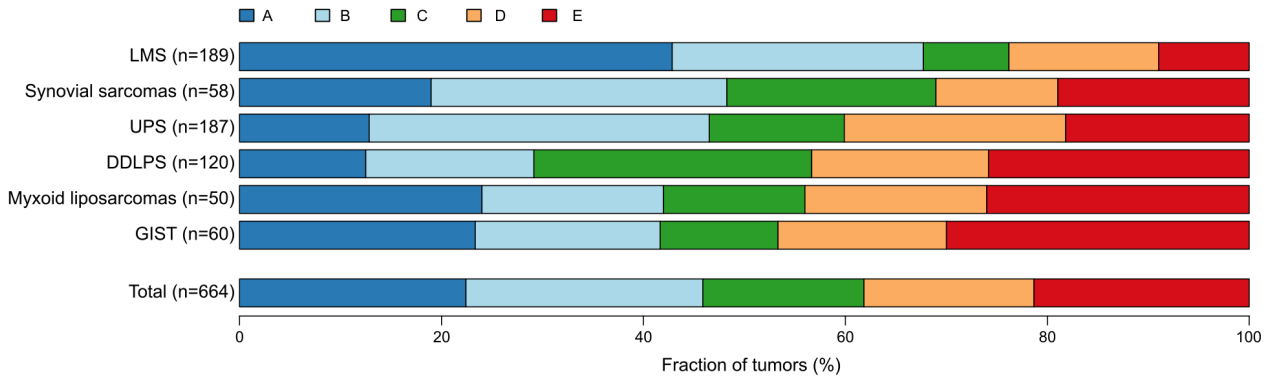
Article

B cells are associated with survival and immunotherapy response in sarcoma

Florent Petitprez[1,2,3,4], Aurélien de Reyniès[4,24], Emily Z. Keung[5,24], Tom Wei-Wu Chen[6,7,8,9], Cheng-Ming Sun[1,2,3], Julien Calderaro[1,10,11], Yung-Ming Jeng[9,12], Li-Ping Hsiao[7], Laetitia Lacroix[1,2,3], Antoine Bougoüin[1,2,3], Marco Moreira[1,2,3], Guillaume Lacroix[1,2,3], Ivo Natario[1,2,3], Julien Adam[13], Carlo Lucchesi[14,15], Yec'han Laizet[14,15], Maud Toulmonde[14,16], Melissa A. Burgess[17], Vanessa Bolejack[18], Denise Reinke[19], Khalid M. Wani[20], Wei-Lien Wang[20], Alexander J. Lazar[20,21], Christina L. Roland[5], Jennifer A. Wargo[5,21], Antoine Italiano[14,16,22], Catherine Sautès-Fridman[1,2,3], Hussein A. Tawbi[23]* & Wolf H. Fridman[1,2,3]*



- Four publicly available datasets:
  - TCGA SARC, Gene Expression Omnibus accessions GSE21050, GSE21122 and GSE30929
- Microenvironment Cell Populations-counter (MCP-counter) method
  - *Becht, Genome Biology, 2016*
- 608 tumors analyzed to create 5 unique, histologi-agnostic Sarcoma Immune Classes (SIC)



Petitprez et al. Nature (2020) 557, 556-560.

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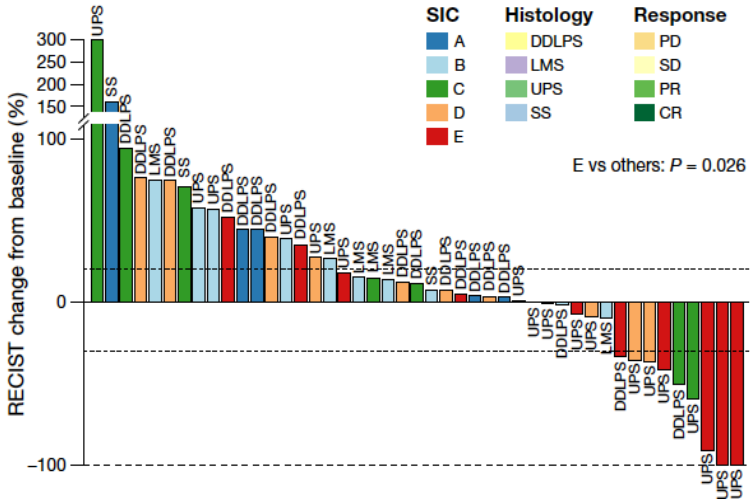
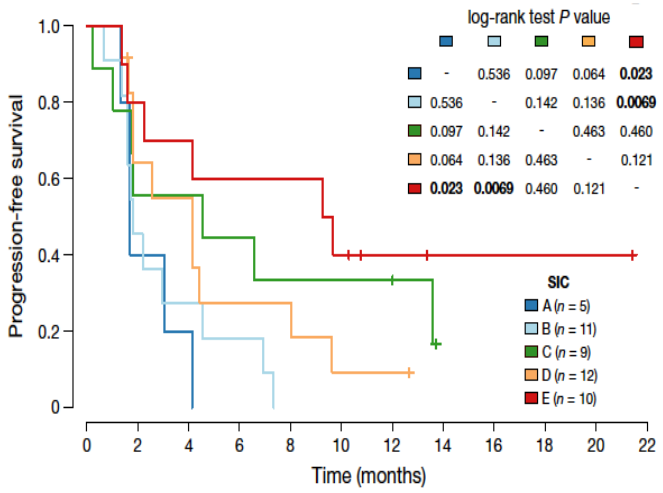
Response to ICB



Progression-Free Survival



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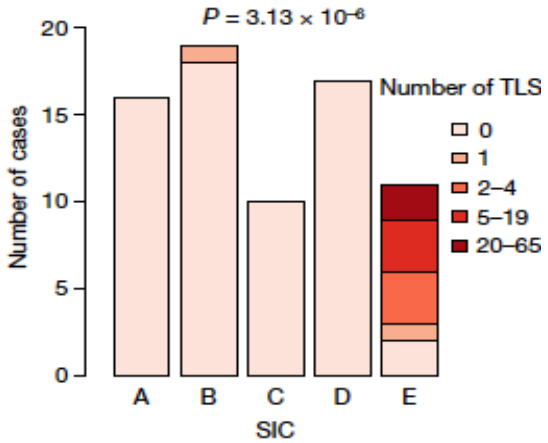
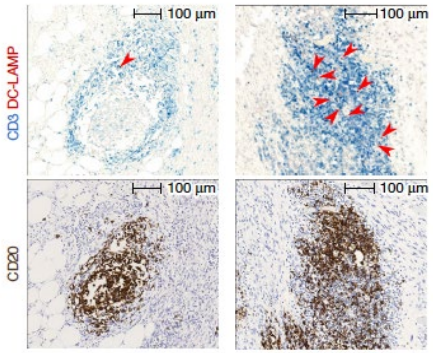
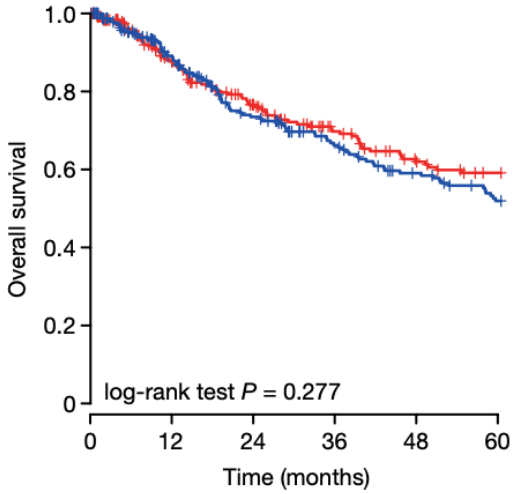
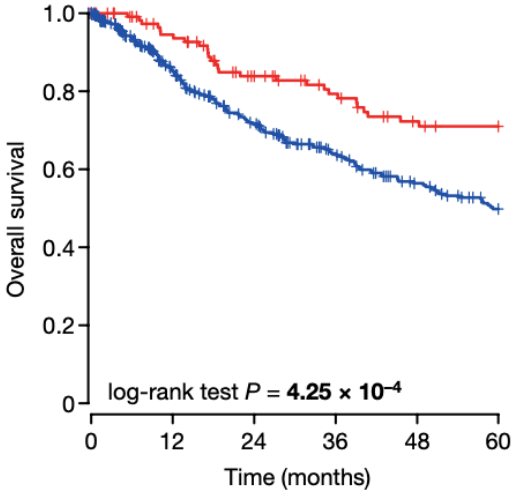
Presence of B cells and tertiary lymphoid structures associated with immune high SIC E signature

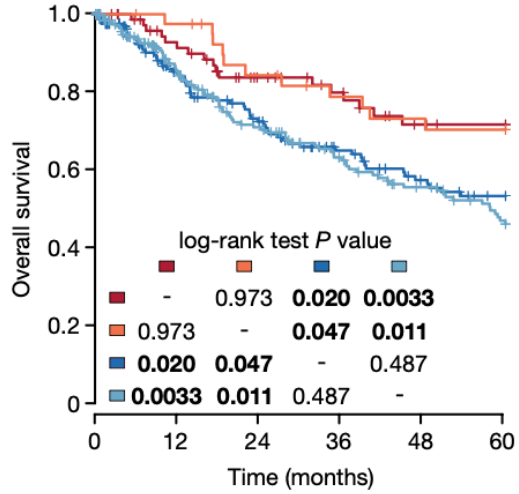




B cell signature associated with improved survival







CD8⁺ T cells
Number at risk

Hi	247	179	139	112	89	78
Lo	249	182	140	113	94	78

B lineage
Number at risk

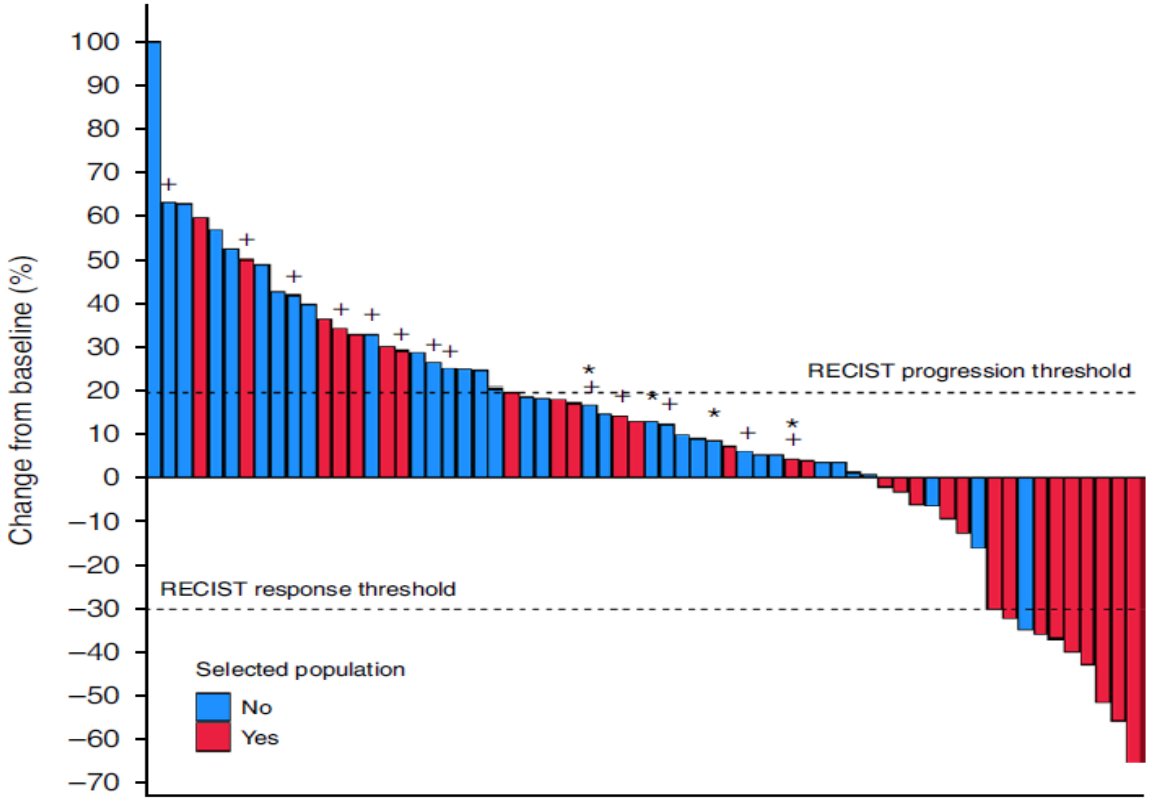
Hi	124	101	80	69	58	55
Lo	372	260	199	156	125	101

B lineage/CD8⁺ T cells
Number at risk

Hi/Hi	82	62	48	41	32	30
Hi/Lo	42	39	32	28	26	25
Lo/Hi	165	117	91	71	57	48
Lo/Lo	207	143	108	85	68	53

Petitprez, Nature, 2020

PEMBROSARC: Using TLS to Select Patients for ICB Treatment

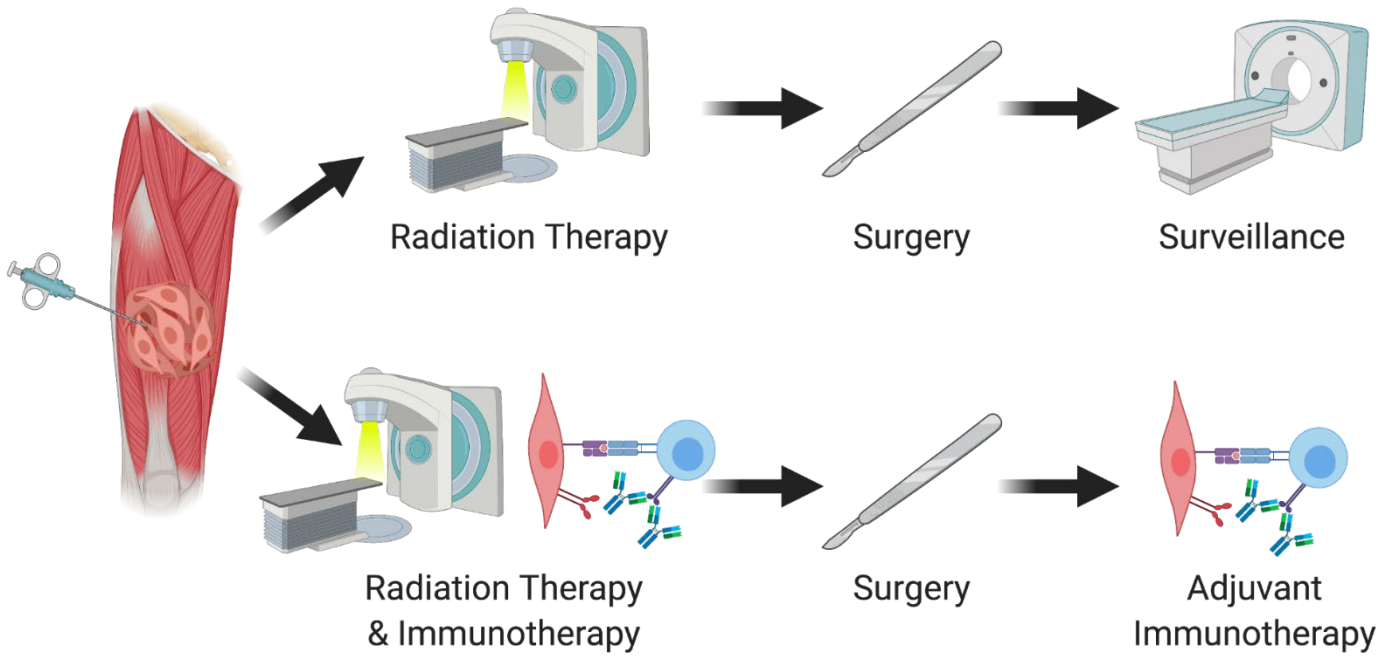


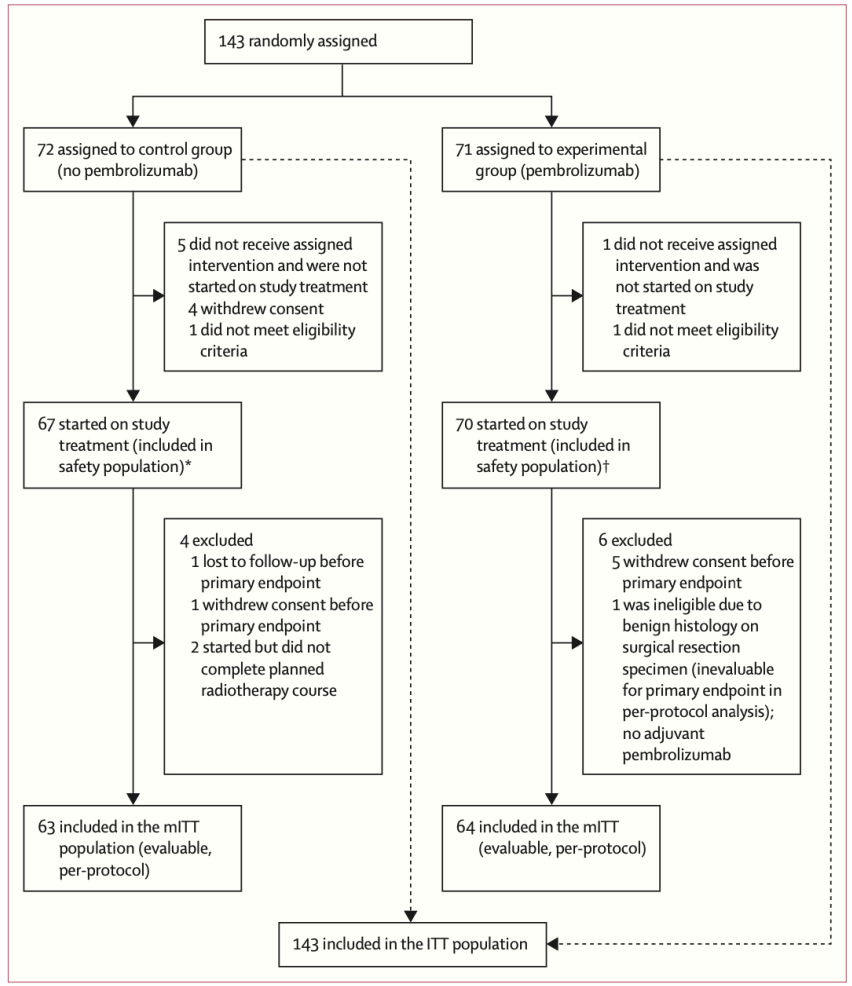
- **All-comer cohorts (n=41)**
  - 6-month NPR 4.9% (95% CI 0.6-16.5%)
  - ORR 2.4% (95% CI 0.1-12.9)
  - Median PFS 1.4 months (95% CI 1.3-2.7)
- **Cohort of patients with intratumoral TLS (n=30)**
  - 6-month NPR 40% (95% CI 22.7-59.40)
  - ORR 30% (95% CI 14.7-49.4)
  - Median PFS 4.1 months (95% CI 1.4-12.5)

Italiano et al. Nature Medicine (2022) 28, 1199-1206.

Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial

Yvonne M Mowery, Karla V Ballman, Angela M Hong, Scott M Schuetze, Andrew J Wagner, Varun Monga, Rachel S Heise, Steven Attia, Edwin Choy, Melissa A Burgess, Susie Bae, David I Pryor, Brian A Van Tine, Gabriel Tinoco, Bartosz Chmielowski, Carolyn Freeman, Alessandro Gronchi, Christian F Meyer, Mark A Dickson, Lee Hartner, Lara E Davis, Benjamin C Powers, Everett J Moding, Kent J Weinhold, Matt van de Rijn, Brian E Brigman, Richard F Riedel, David G Kirsch





Mowery et al. Lancet (2024) 404, 2053-2064.

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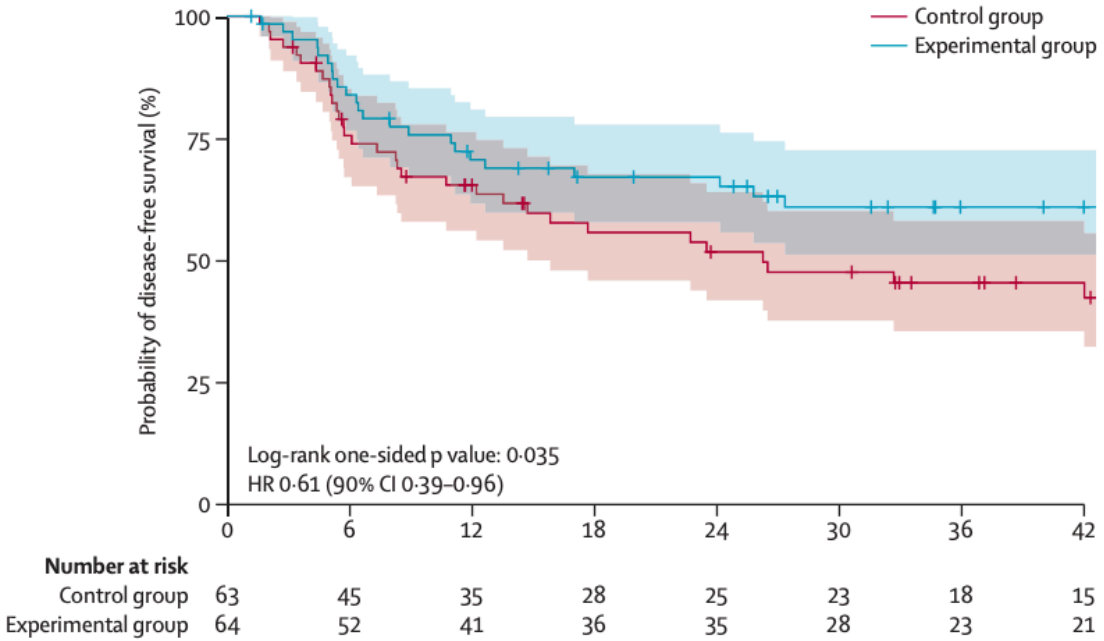
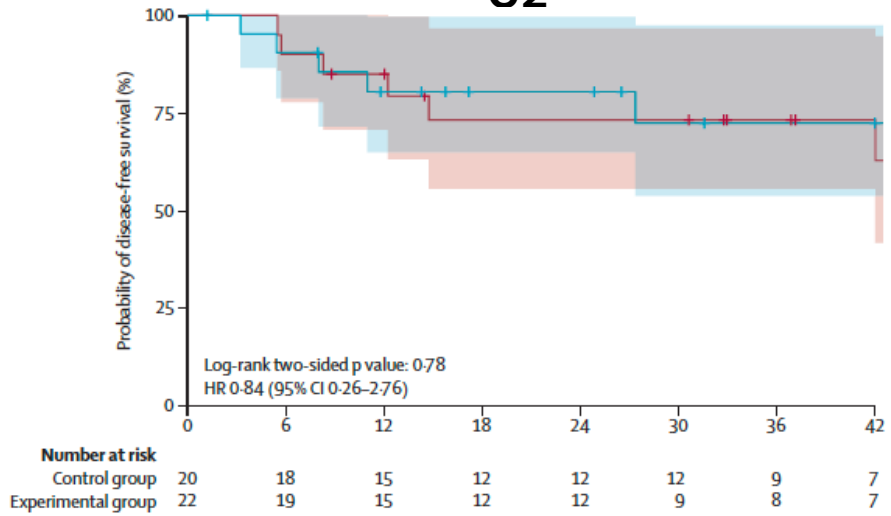
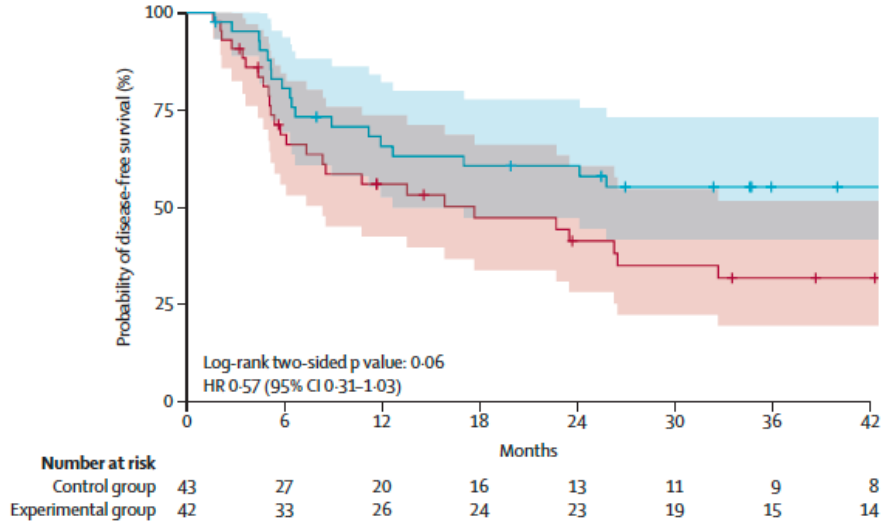
- **2-year DFS: 67% vs 52%**
- Median f/u: 43 months
- 56 events: 24 experimental, 32 control



G2



G3



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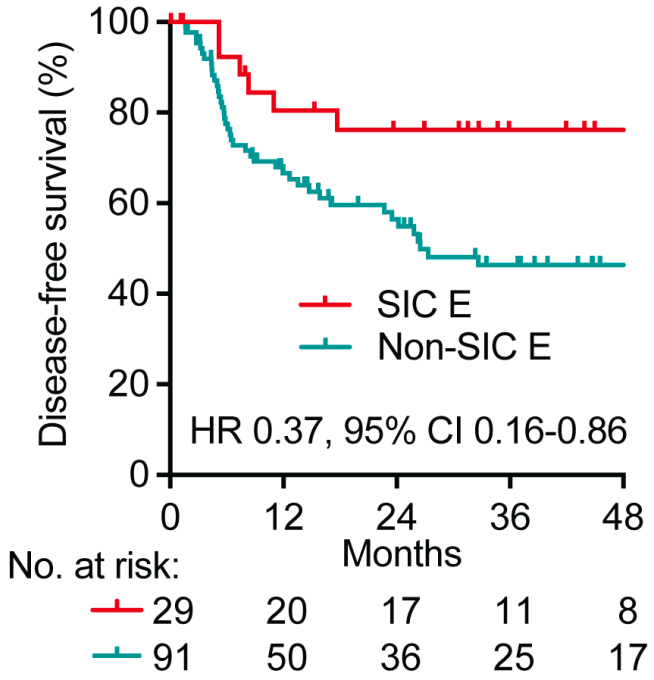
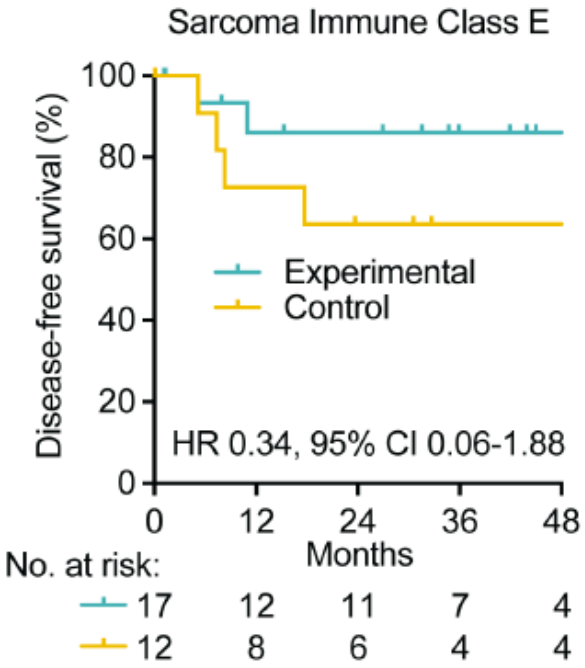
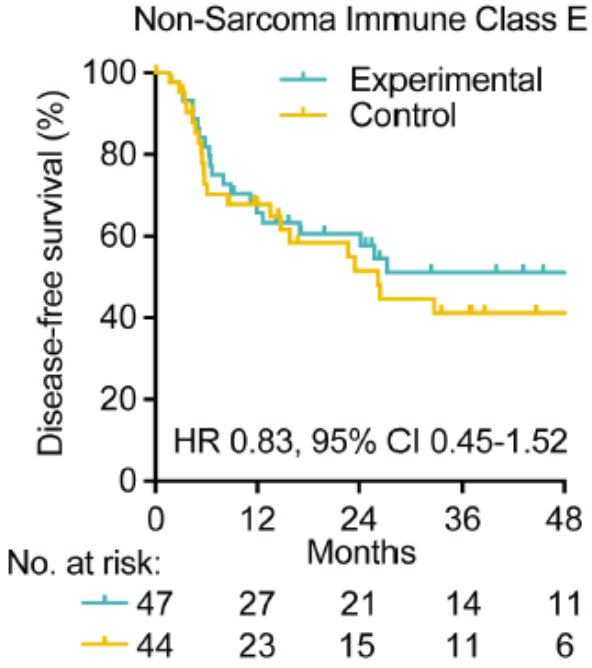
Association of SIC E and ICB Response in SARC032

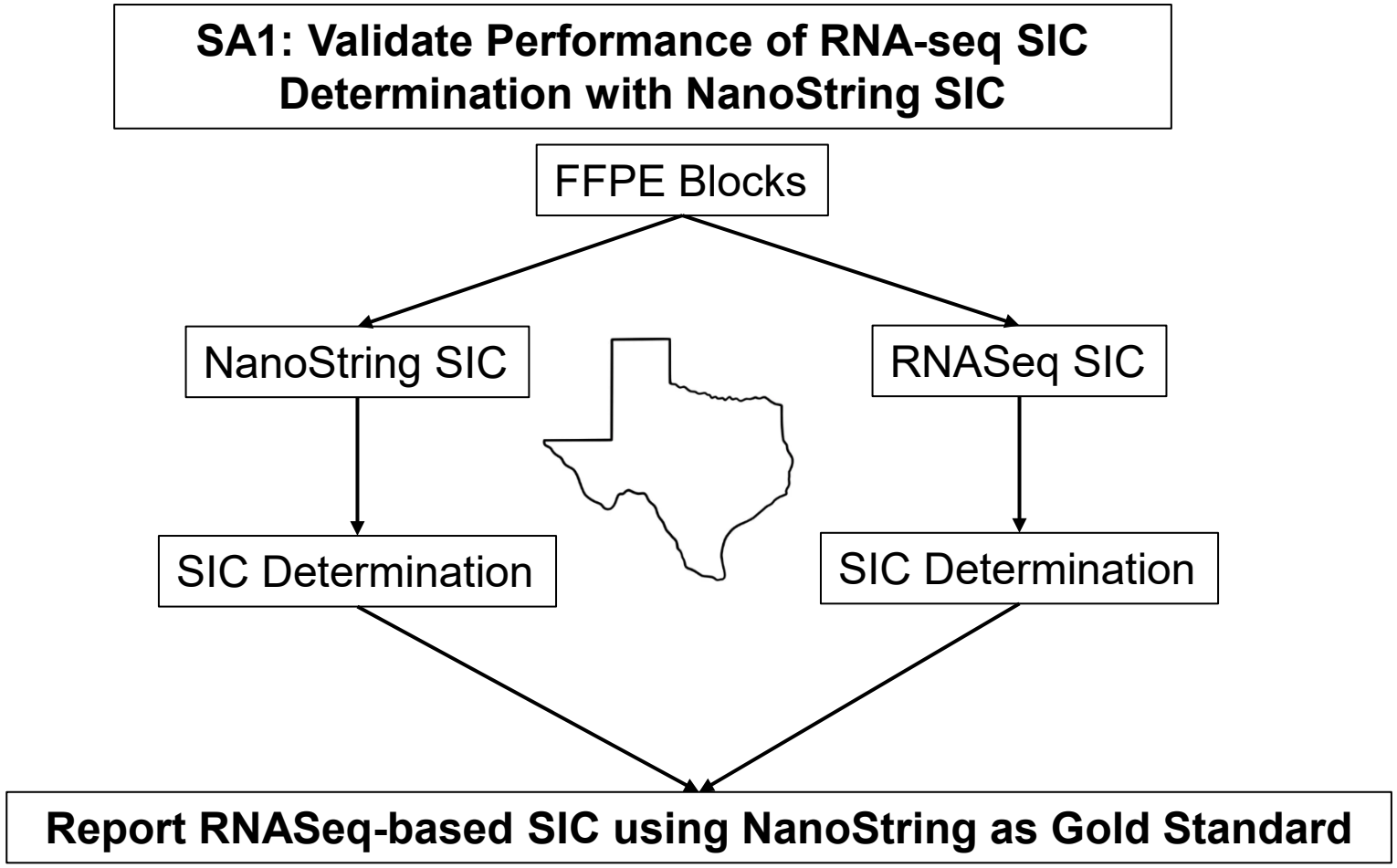






CTOS 11/16/24 presentation by Dr. David Kirsch

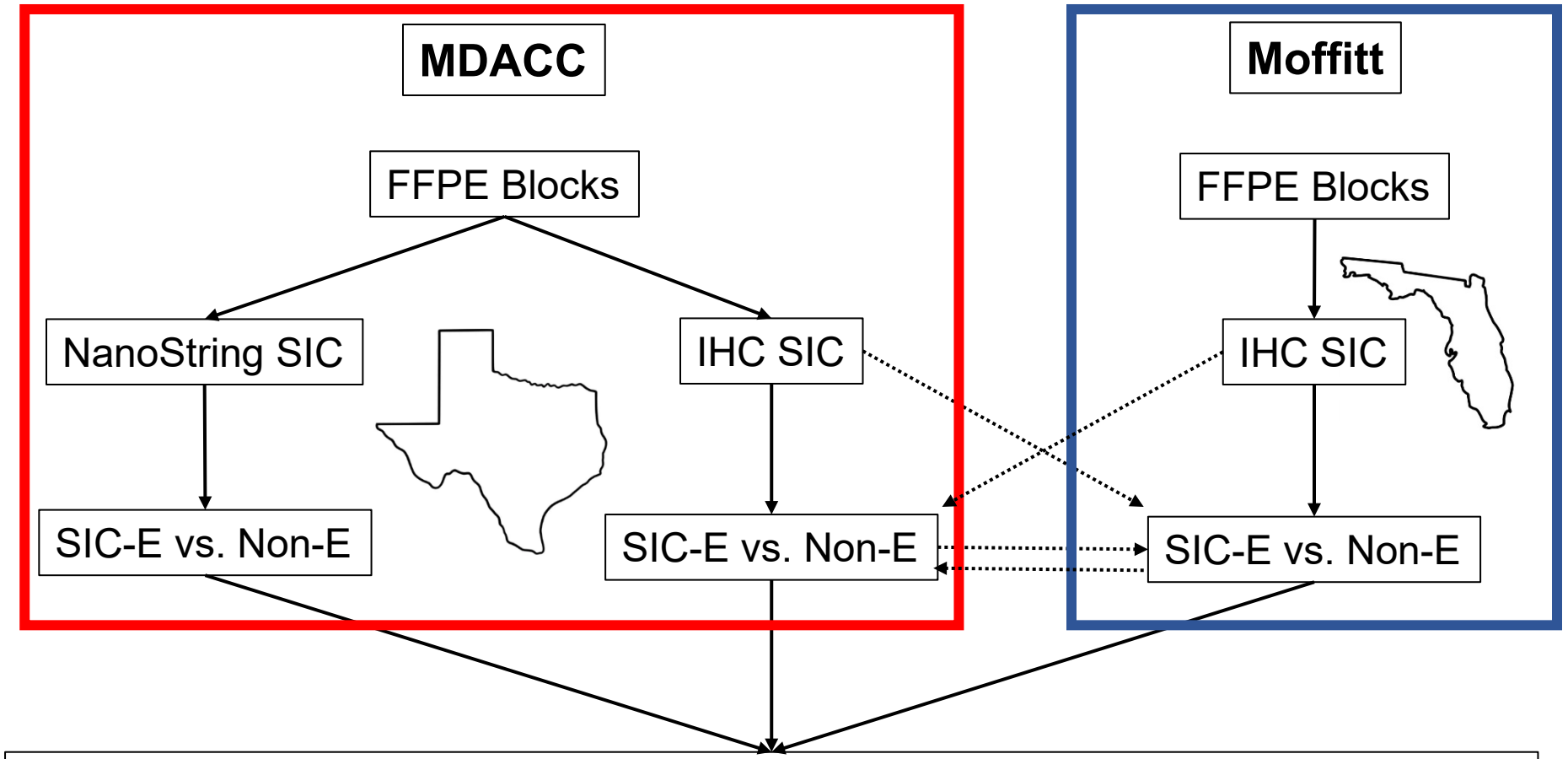
Grant Proposal for SOC assessment of SIC



- **PI: Emily Keung, MDACC**
- **Co-I: John Mullinax, Moffitt**
- **Collaborators: Alex Lazar (pathology), Lulu Shang (biostatistics), Florent Petitprez**

Grant Proposal for SOC assessment of SIC

SA2: Develop IHC-Based Surrogate for NanoString SIC E vs non-E



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Summary:

- T-cell infiltrate alone does not predict outcome
  - SIC E describes a group of STS with high B&T-cell infiltrate
  - Approx 20% of all STS subtypes
  - Strongly correlated with outcome

- Future soft tissue sarcoma trial design should include SIC status as consideration in eligibility criteria
  - ? Cohort stratification
  - ? Strict inclusion criteria

- STRASS3
  - If this will include evaluation of any immunotherapy approach, recommend stratifying by SIC rather than histologic subtype
  - Will likely enrich for DDLPS

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