Immune Phenotype-Dependent Pembrolizumab Effects in High-Risk Localized Soft Tissue Sarcoma: A multimodal and explainable machine learning analysis of SARC032 trial data

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Significance & Hypothesis/Techniques

Pembrolizumab added to neoadjuvant radiotherapy significantly improved disease-free survival (DFS) in patients with grade 3 soft tissue sarcoma in the SU2C-SARC032 trial[1]. However, the benefit appeared heterogeneous, suggesting that not all patients derive equal advantage from immunotherapy. This study addresses a critical knowledge gap: the lack of reliable biomarkers to identify which patients with high-risk localized soft tissue sarcoma will benefit from the addition of pembrolizumab. The goal was to determine whether treatment effects are modified by sarcoma immune class (SIC), particularly SIC E status[2], using multimodal explainable machine learning (ML) to predict 1-year DFS. By modeling immune phenotype–treatment interactions, this AI-driven approach aims to move towards personalized, biomarker-driven immunotherapy in sarcoma.

Innovation

This is the first application of explainable ML techniques (LightGBM and SHAP values) to integrate clinical variables with the novel sarcoma immune class (SIC) biomarker from the SARC032 trial. The explicit modeling of treatment and immune phenotype interactions demonstrates that pembrolizumab benefit may be immune phenotype-dependent rather than uniform. Clinically, it provides a framework for refining patient selection, potentially sparing non-responders from unnecessary immunotherapy toxicity while identifying those most likely to benefit.

Approach (Materials & Methods)

We conducted a secondary analysis of SARC032 participants with complete data for 1-year DFS (analytic cohort: n=100 after exclusions for incomplete data or <1-year follow-up). Candidate features included baseline clinical variables (age, sex, tumor necrosis, tumor grade, tumor size, tumor location), pembrolizumab treatment assignment, and sarcoma immune class (SIC) E status. We evaluated logistic regression (with interaction terms), Cox proportional hazards, and Light Gradient Boosting Machine (LightGBM) models. Models were trained with 5-fold stratified cross-validation and performance estimated using 1,000 bootstrap resamples to generate 95% confidence intervals. Discrimination was measured by ROC-AUC, PR-AUC, and C-index. Model explainability was assessed via permutation-based feature importance and SHAP values.

Results

Logistic regression achieved the highest performance with clinical variables plus pembrolizumab treatment and SIC E status (ROC-AUC 0.65, 95% CI 0.53–0.78; PR-AUC 0.44, 95% CI 0.30–0.64). Addition of pembrolizumab alone did not improve performance. LightGBM models performed best with clinical features alone or with SIC E (ROC-AUC 0.67, 95% CI 0.55–0.77), with inclusion of SIC E improving discrimination. In survival analysis, the Cox model with all features and treatment–immune interaction yielded the highest C-index (0.75, 95% CI 0.68–0.82). The strongest feature contributions were tumor location, sex, SIC E status, and the interaction between SIC E status and treatment with Pembrolizumab.

Across all models, inclusion of SIC E generally improved model performance, whereas pembrolizumab as a standalone feature did not.

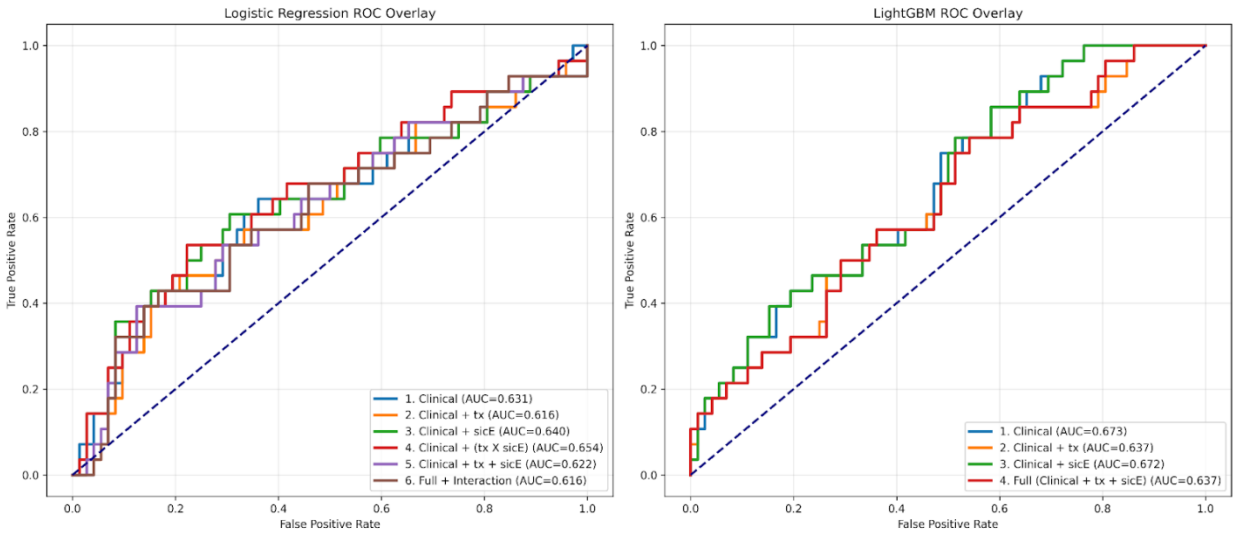
Discussion & Impact

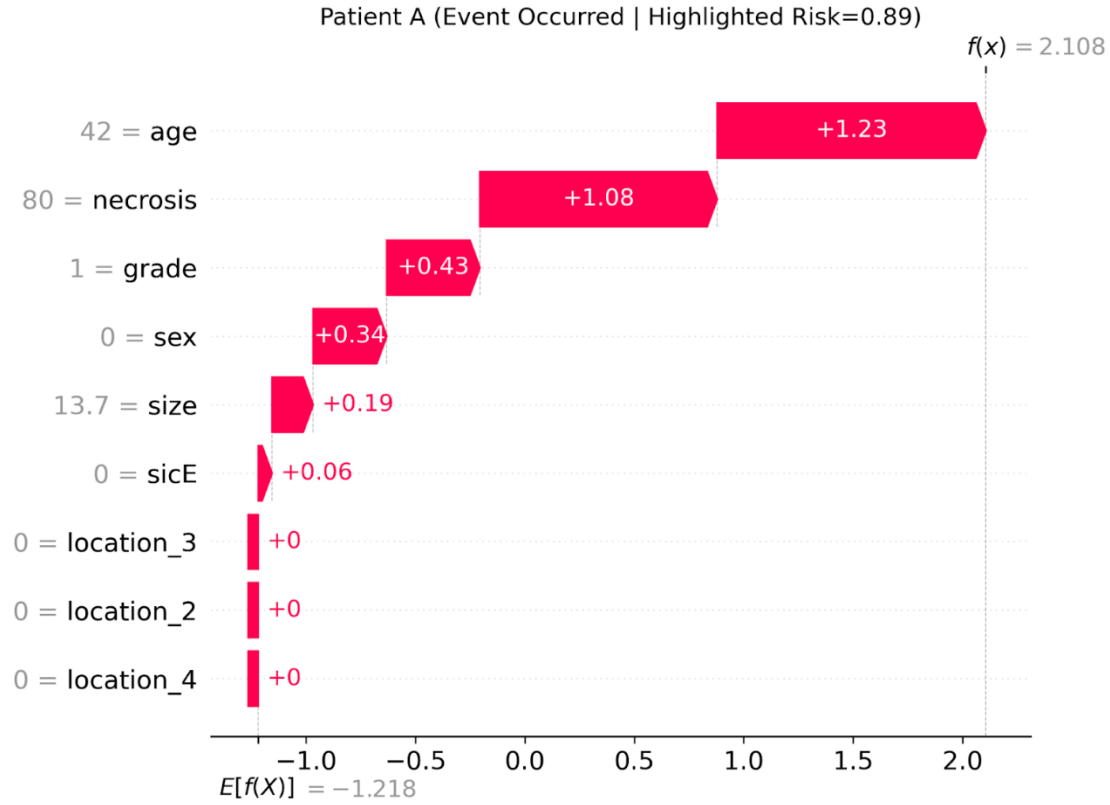
These ML models demonstrated modest but meaningful discrimination for 1-year DFS and time-to-event outcomes. The enhanced performance when explicitly modeling treatment-by-immune phenotype interactions, combined with the absence of a stable main effect of pembrolizumab alone, indicates that immunotherapy benefit in high-risk localized soft tissue sarcoma is heterogeneous and dependent on the tumor immune microenvironment. This refines the population-level findings of SARC032 and supports biomarker-driven patient selection using SIC.

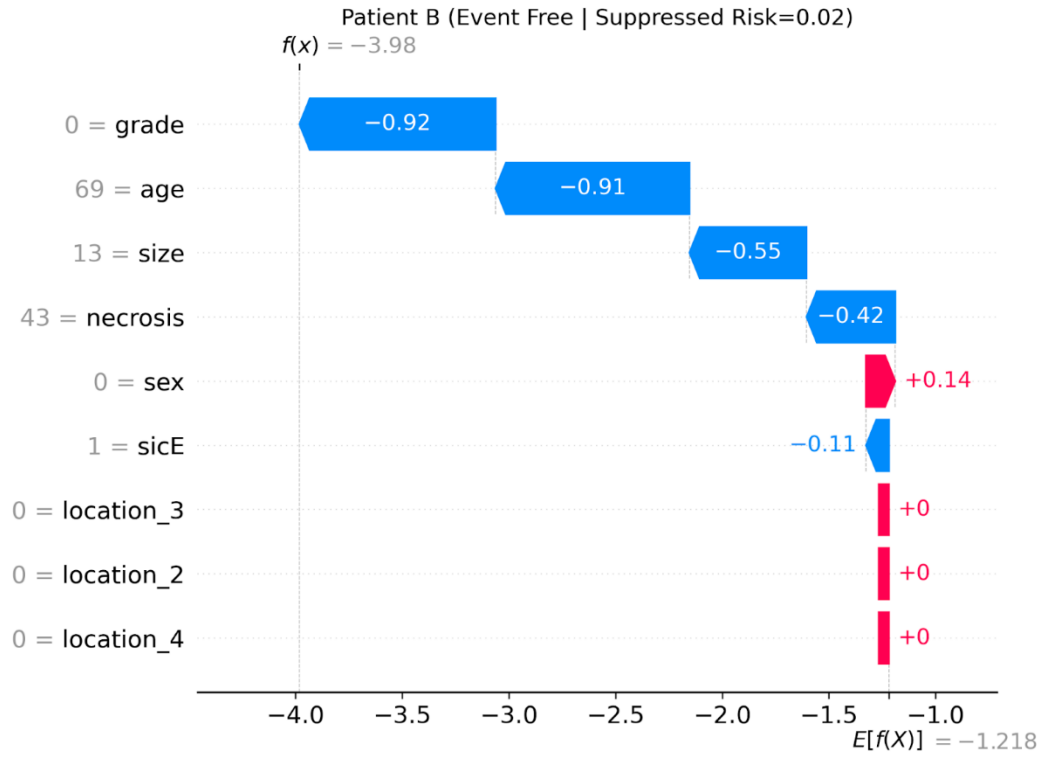
References:

1. Mowery, Y. M., Ballman, K. V., Hong, A. M., Schuetze, S. M., Wagner, A. J., Monga, V., ... & Kirsch, D. G. (2024). 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. The Lancet, 404(10467), 2053-2064.
2. Testa, S., Himes, J. E., Subramanian, A., Nouth, S. C., Ballman, K. V., Heise, R. S., ... & Moding, E. J. (2025). Distinct Sarcoma Microenvironments Predict Benefit from Addition of Pembrolizumab to Preoperative Radiotherapy and Surgery in SU2C-SARC032. medRxiv, 2025-11.

Figures:




Patient A (Event Occurred | Highlighted Risk=0.89)
f(x) = 2.108
42 = age
80 = necrosis
1 = grade
0 = sex
13.7 = size
0 = sicE
0 = location_3
0 = location_2
0 = location_4
+1.23
+1.08
+0.43
+0.34
+0.19
+0.06
+0
+0
+0
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0
E[f(X)] = −1.218


Patient B (Event Free | Suppressed Risk=0.02)
f(x) = −3.98
0 = grade
69 = age
13 = size
43 = necrosis
0 = sex
1 = sicE
0 = location_3
0 = location_2
0 = location_4
−0.92
−0.91
−0.55
−0.42
+0.14
−0.11
+0
+0
+0
−4.0
−3.5
−3.0
−2.5
−2.0
−1.5
−1.0
E[f(X)] = −1.218