

11539: Circulating free DNA derived from active chromatin as a predictive biomarker for clinical benefit to checkpoint inhibitor-based therapies in metastatic leiomyosarcoma

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Background

- Leiomyosarcoma (LMS) is a soft tissue sarcoma subtype with poor prognosis in the metastatic setting.
- Combinatorial checkpoint inhibitor (CPI) therapy may provide benefit, possibly due to enriched epigenetic alterations.
- This study applies a novel active chromatin cell-free DNA (cfDNA_{ac}) platform to profile LMS patients receiving CPI-based therapies (durvalumab + olaparib or cediranib) in the DAPPER phase 2 trial (NCT03851614).
- Specific Aims:**
 - Leverage a novel liquid biopsy platform to enrich and extract cfDNA_{ac} to identify molecular features associated with clinical outcomes, including:
 - Clinical Benefit Rate (CBR): partial response or stable disease >6 months
 - Progression-Free Survival (PFS)
 - Evaluate other cfDNA_{ac} feature that can serve of biomarkers of clinical outcomes

Methods

- Baseline plasma samples were collected during the DAPPER trial¹ (Figure 1a) and subsequently processed according to the cfDNA_{ac} workflow (Figure 1b-c).

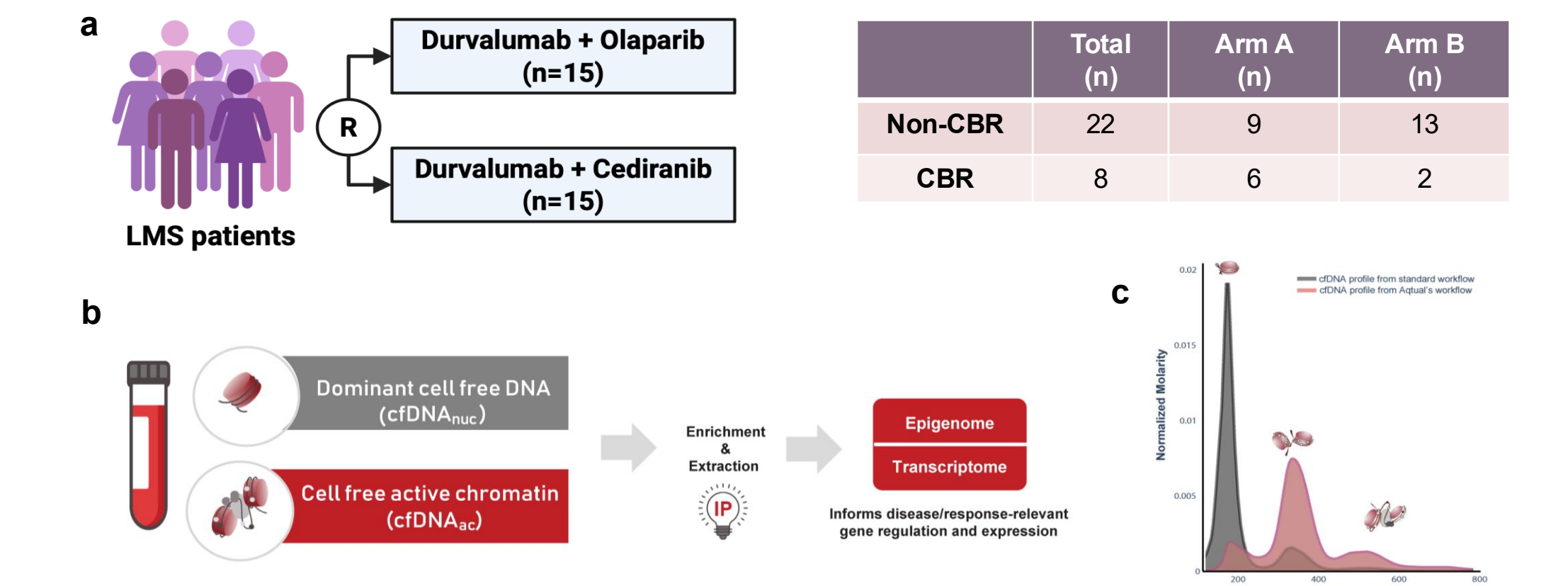


Figure 1: (a) Overview of the DAPPER trial; (b) cfDNA_{ac} enrichment and extraction workflow; (c) Feature analysis to evaluate cfDNA_{ac}-derived molecular profiles and their correlation with clinical outcomes (CBR and PFS); (c)

Results

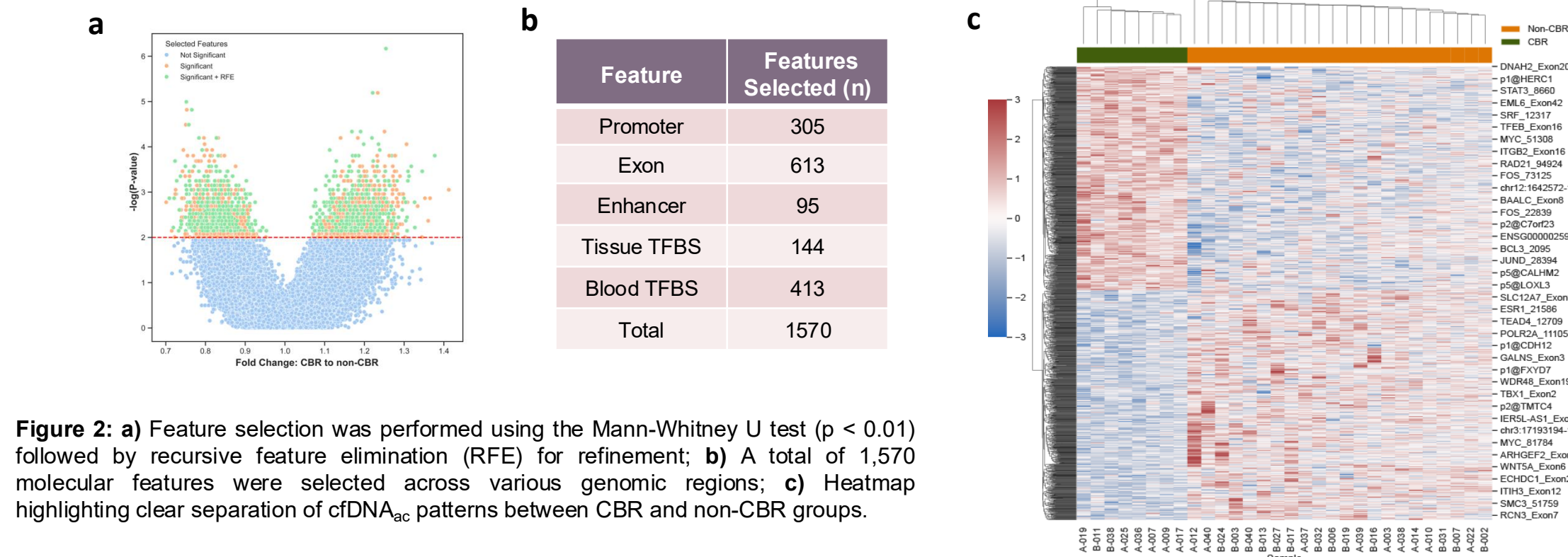


Figure 2: a) Feature selection was performed using the Mann-Whitney U test (p < 0.01) followed by recursive feature elimination (RFE) for refinement; b) A total of 1,570 molecular features were selected across various genomic regions; c) Heatmap highlighting clear separation of cfDNA_{ac} patterns between CBR and non-CBR groups.

Results

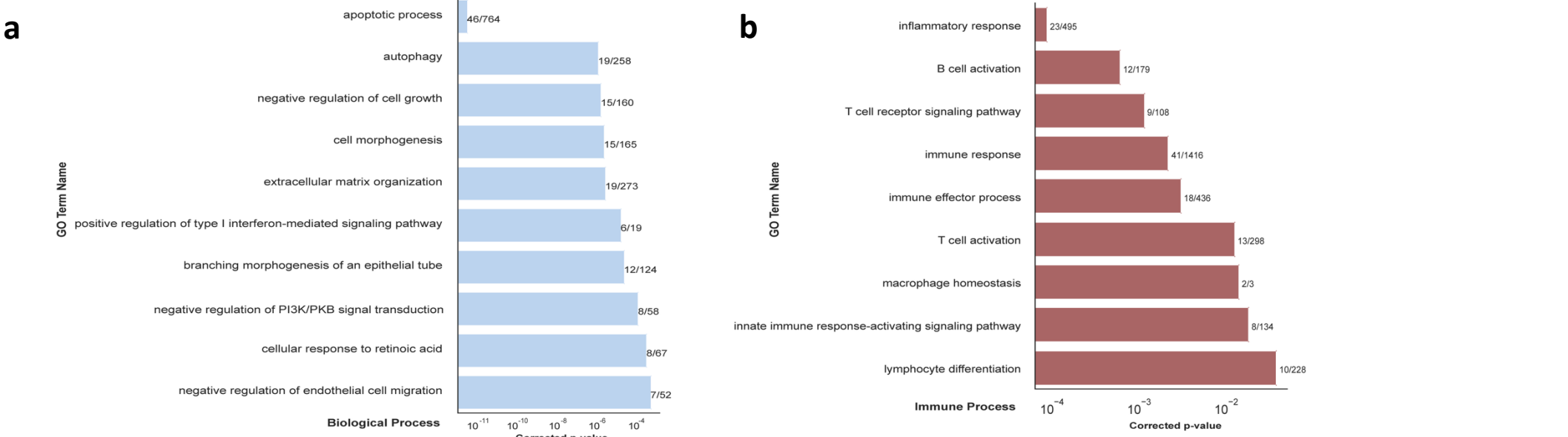


Figure 3: Over-representation analysis of (a) Gene Ontology biological processes and (b) immune-related gene sets reveals significant enrichment of cell death pathways, interferon-gamma signaling, and activation of innate and adaptive immune responses in CBR patients.

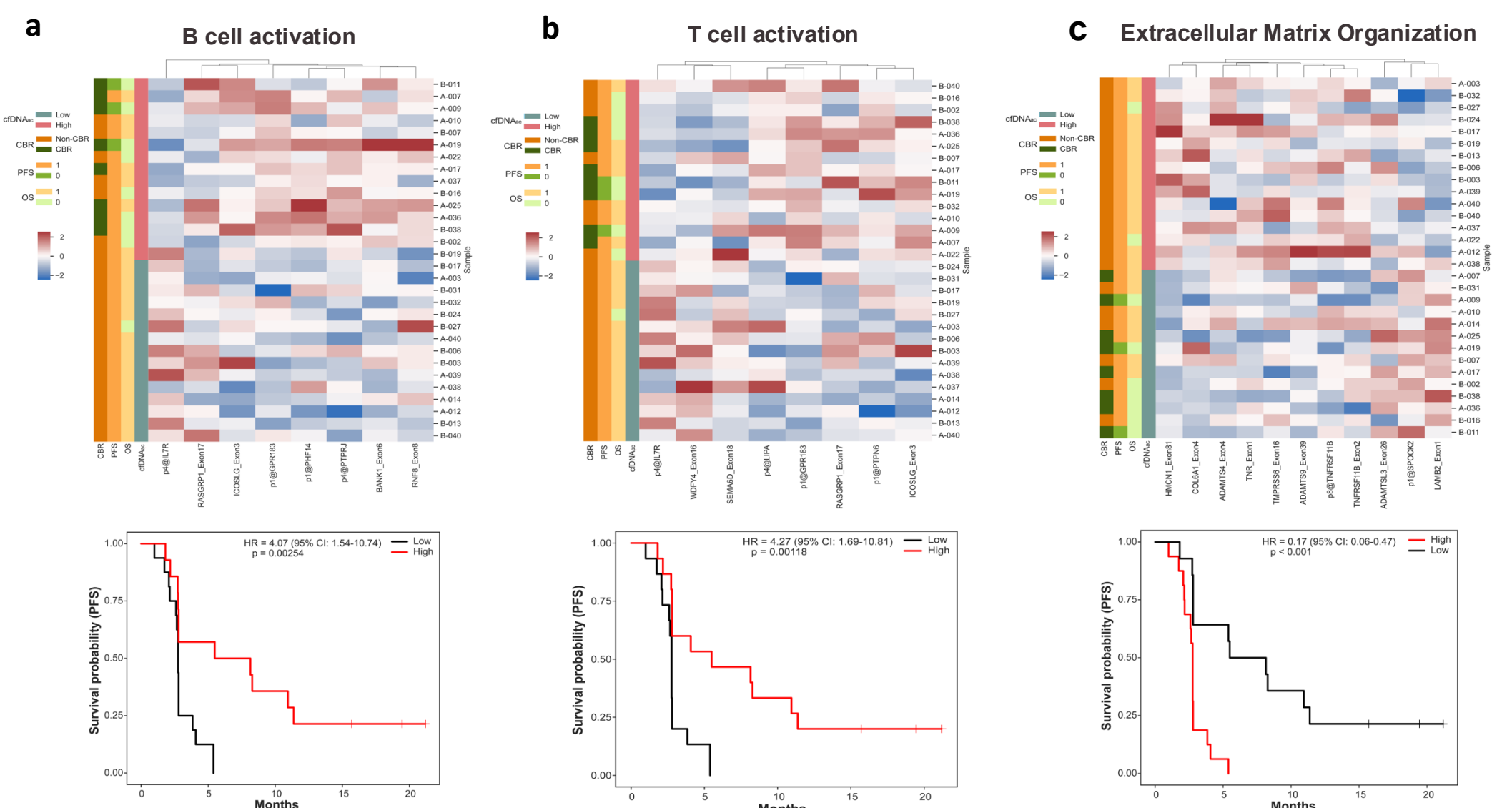


Figure 4: Immune-enriched signatures based on cfDNA_{ac} signals and clinical outcomes. Heatmaps show the distribution of patient clinical outcomes stratified by (a) B cell activation, (b) T cell activation, and (c) extracellular matrix organization signatures. All signatures are significantly associated with progression-free survival (PFS) after adjusting for false discovery rate (FDR) using the Benjamini-Hochberg method (p < 0.05). Corresponding Kaplan-Meier curves illustrating PFS associations are shown below each heatmap.

Conclusions

- Our results demonstrate that cfDNA_{ac} detection is feasible in plasma samples of metastatic LMS patients undergoing combinatorial checkpoint inhibitor therapy.
- Transcriptomic signatures derived from cfDNA_{ac} effectively differentiate patients who experience clinical benefit (CBR) from non-responders.
- Notably, CBR patients exhibit enrichment of anti-proliferative and immune-related pathways. Molecular signatures— including B-cell activation, T-cell activation, and extracellular matrix organization— are specifically associated with both clinical benefit and prolonged progression-free survival (PFS).
- Genome-wide copy number variation (CNV) derived from cfDNA_{ac} exhibits patterns consistent with those observed in tissue gDNA-derived CNV.³ Higher baseline tumor fraction measured by cfDNA_{ac} is associated with reduced clinical benefit and shorter progression-free survival.
- A distinct CNV profile derived from cfDNA_{ac} distinguished patients who achieved clinical benefit from non-responders and was significantly associated with PFS.

References

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