Abstract #12 | Poster

Niche eviction via CD49d targeting sensitises BM-tropic DLBCL to CD3×CD20 bispecifics.

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Background
Diffuse large B-cell lymphoma (DLBCL) is the most prevalent aggressive non-Hodgkin lymphoma in adults. Bone marrow (BM) involvement signals poor outcomes, stromal protection and immune exclusion that may limit T-cell-redirecting immunotherapies. CD49d/VLA-4 (ITGA4), via VCAM-1 and extracellular matrix, mediates malignant B-cell adhesion and survival in these immune-restricted niches.

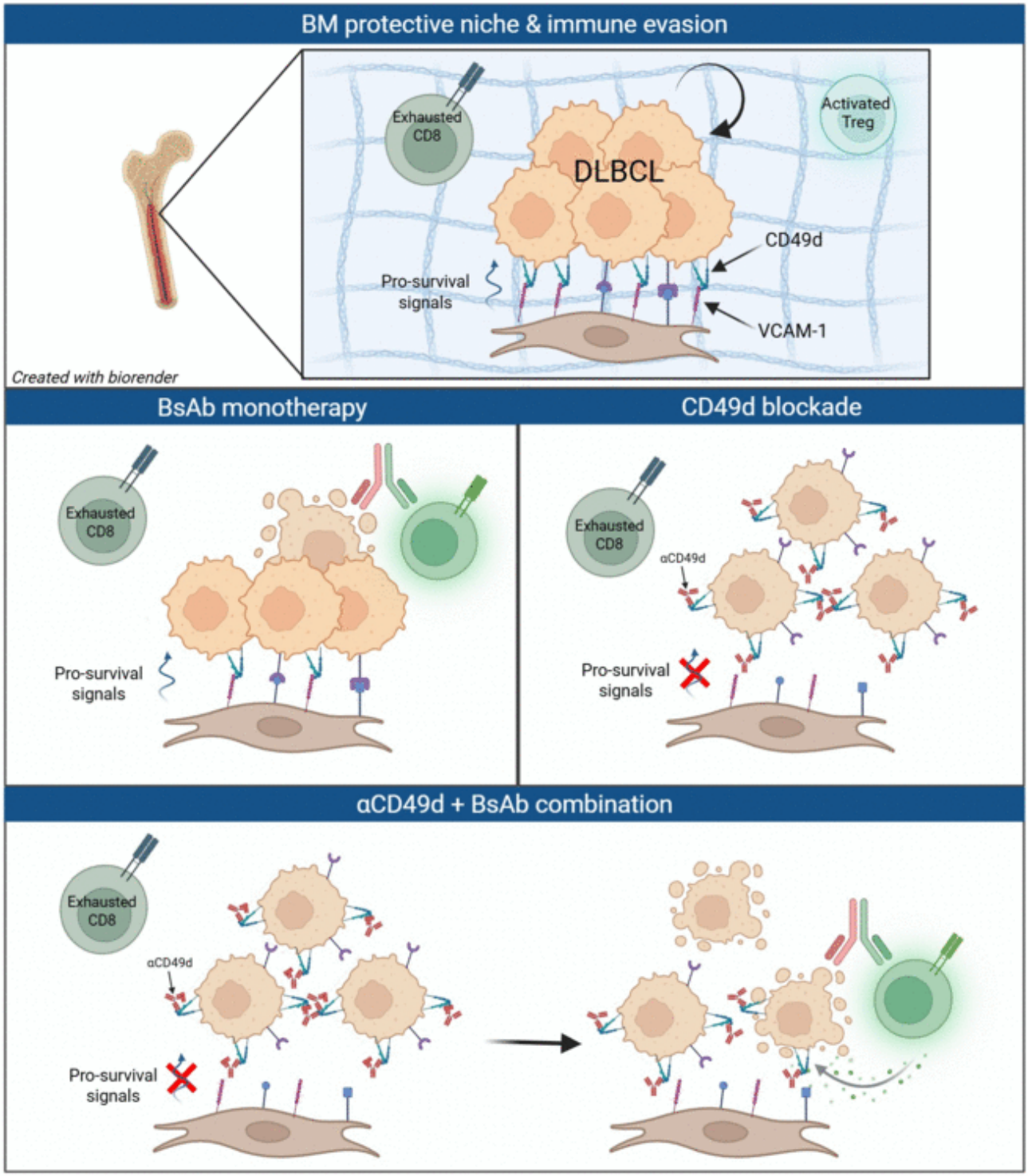
Aims
This study investigates whether targeting the integrin CD49d can evict lymphoma cells from protective niches and sensitise them to CD3×CD20 bispecific killing.

Methods
We used a novel transplantable DLBCL mouse model (DCGL), spontaneously arising from T-cell lymphoma passage in C57BL/6 mice. This model reaches end-stage disease within 2 weeks, primarily involving BM, spleen, and liver. The immune landscape was characterized by spectral flow cytometry. We tested CD3×CD20 BsAb in combination with anti-CD49d blockade, elucidating mechanism via in vivo Fc-receptor blocking. Clinical relevance of CD49d was assessed by investigating its expression in DLBCL patient samples and correlating gene expression to survival in TCGA database.

Results
Disease progression in the DCGL model was marked by rapid tumor expansion, global immune activation, and progressive CD8+ T-cell exhaustion. While CAR-T efficacy was restricted by rapid tumor expansion, BsAb monotherapy significantly reduced tumor load within the BM but had limited peripheral impact. Conversely, anti-CD49d monotherapy induced dramatic tumor clearance in the spleen and liver through Fc-independent mechanism but showed more limited BM efficacy, suggesting a mechanism based on disrupting tumor-microenvironment interactions to promote mobilization. Consequently, the combination synergistically reduced tumor load across all compartments and significantly prolonged survival (HR = 0.13 [0.025-0.66], p = 0.014). In patients, high CD49d expression was identified in 5/17 lymph node samples and correlated with poor survival.

Summary/Conclusion
CD49d targeting mobilizes DLBCL cells, abrogating niche survival signals. Despite systemic T-cell activation, the BM microenvironment remains T-cell poor with effector exclusion, limiting CD3×CD20 BsAb access. CD49d blockade overcomes this immune restriction, unlocking bispecific potential in this sanctuary site. This combinatorial strategy potently debulks CD49d+ BM-involved DLBCL, overcoming protective niche resistance.

Keywords: DLBCL – CD49d/VLA-4 – CD3xCD20 bispecific – BM niche



aCD49d + aCD3/aCD20 BsAb synergy in the bone marrow