ELSEVIER

Blood 142 (2023) 6124–6126

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

Intensity of Survivin Expression Correlates with Clinical and Biological Markers of Aggressive R/R DLBCL

Sila Usta, BSc[1], Alexandra Misura, BSc[1], Kim Roos[2], Iran Rashedi, MDPhD[2], Irina Amitai, MD[3], Yidi Jiang[2], Kathryn Mangoff[2], Gail Klein[2], Nicholas Allen Forward, MD[4], Douglas A. Stewart, MD[5], Joy Mangel, MD[6], George A. Tomlinson, PhD[7], Hubert Tsui, MD PhD FRCPC[8], Neil Berinstein, MD FRCPC[9]

[1] Precision Diagnostics and Therapeutics Program, Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, Canada
[2] Sunnybrook Research Institute, Toronto, CAN
[3] Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4] Queen Elizabeth II Health Sciences Centre, Halifax, Canada
[5] Tom Baker Cancer Centre and University of Calgary, Calgary, Canada
[6] London Health Sciences Ctr., London, CAN
[7] Toronto General Hospital Eaton North Wing, Toronto, CAN
[8] Division of Hematological Pathology, Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Toronto, Canada
[9] Sunnybrook Health Sciences, Odette Cancer Centre, Toronto, Canada

Introduction: The SPiReL phase II clinical trial evaluated combination immunotherapy with an immunogenic vaccine formulation to the tumor antigen survivin comprised of maveropepimut-S (MVP-S), pembrolizumab and cyclophosphamide in survivin-expressing relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL). The efficacy of this survivin-directed T cell educating therapy may be influenced by the survivin antigen burden in the DLBCL. To further explore this potential relationship, we evaluated the heterogeneity of tumor survivin expression in the SPiReL study cohort and its associations with established clinical-pathological DLBLC variables.

Methods: Survivin immunohistochemistry (IHC) was performed at NeoGenomics Laboratories (Aliso Viejo, California, USA) on formalin fixed paraffin embedded (FFPE) tumor slides from diagnostic biopsies obtained at trial screening. Inclusion criteria stipulated >10% of tumor cells expressing survivin by IHC. Semi-quantitative survivin expression metrics, as determined by pathologist assessment, included: total percentage of survivin-positive cells; intensity of survivin staining scored as 0 = None, 1+ = Weak, 2+ = Moderate, 3+ = Strong; and H-score, a linear weighted average (% positive cells x staining intensity level). Radiologic tumor burden was measured at up to 4 time points during the trial by computed tomography (CT). Other pathology (e.g. cell of origin) and laboratory biomarkers (e.g. lactate dehydrogenase, LDH) were extracted from clinical results.

Results: The mean and median percentage of survivin-positive tumor cells for all enrolled participants (n= 25) was 91% and 99%, respectively. At the per participant level, the range of survivin expression was 50-100% of the cellular content. The heterogeneity of survivin expression intensity among participants is shown in Figure 1. All participants had some proportion of biopsied cells expressing strong (3+) intensity survivin (range: 5-100% of cells, mean: 30% while only 52% of tumors contained non-survivin expressing (0) cells, ranging from 0% to 50% (mean: 9%)

Greater proportions of cells that expressed moderate (2+) and/or strong (3+) survivin significantly correlated with clinical and biological markers of aggressive DLBCL. Non-GCB tumours (11/25) showed greater H-scores compared to GCB tumours (212 vs 167, p = 0.0287). Non-GCB tumours contained greater proportions of strong intensity (3+) survivin cells compared to GCB tumours (44% vs 25%, p= 0.045).

In addition, participants with LDH above the upper limit of normal at screening (52%, 13/25) had a greater mean proportion of cells expressing moderate and strong intensity survivin (proportion of 2+ and 3+ combined) (72% vs 54%, p = 0.0447) and a lower mean proportion of weak survivin intensity (1+) cells (p = 0.0374) compared to those with normal LDH.

A relationship between total tumor area at baseline and survivin intensity levels was explored. Higher proportions of cells expressing weak intensity (1+) survivin were associated with smaller total tumour area at baseline (p=0.0201). In contrast, higher combined proportions of moderate (2+) and high (3+) intensity survivin was associated with larger total tumour area at baseline (p=0.0285).

The significant association with the 2+/3+ intensity of survivin with LDH, cell of origin and tumour burden may suggest a mechanistic threshold in DLBCL pathobiology that drives aggressive clinical behavior.

Discussion: Here we demonstrate substantial heterogeneity of survivin protein expression in baseline tumour biopsies of R/R DLBCL patients. Given our findings, it may be of clinical and pathobiological significance to assess both the proportion of survivin-expressing cells as well as the intensity of survivin expression. As the known functions of survivin include protection from apoptosis and cell-cycle progression, the associations demonstrated here support the relevance of survivin and in particular high intensity (2+, 3+) survivin as a biomarker linked with aggressive R/R DLBCL features. These results further support the targeting of survivin pathways in interventional trials and development of validated clinical laboratory survivin assays. Further analysis by multiplex immunofluorescence is in progress to further explore how 2+/3+ vs. 0 host immune cells may also influence survivin immunogenicity and clinical response post-MVP-S immunotherapy.

Disclosures Forward: *ADC Therapeutics:* Research Funding; *BeiGene:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen,:* Membership on an entity's Board of Directors or advisory committees; *IMV:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *MorphoSys:* Research Funding; *Astellas:* Research Funding; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Kite/Gilead:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *InCyte:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS/Celgene:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *SeaGen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Stewart:** *Teva:* Honoraria; *Amgen:* Honoraria; *Celgene:* Honoraria; *Gilead:* Honoraria; *Abbvie:* Honoraria; *Novartis:* Honoraria; *AstraZeneca:* Honoraria; *Janssen:* Honoraria; *Roche:* Honoraria; *Sandoz:* Honoraria. **Tsui:** *LifeLabs:* Consultancy; *Precision Dx:* Consultancy; *Novartis:* Honoraria. **Berinstein:** *Astra Zeneca:* Other: Scientific Advisor, Research Funding.

https://doi.org/10.1182/blood-2023-189200

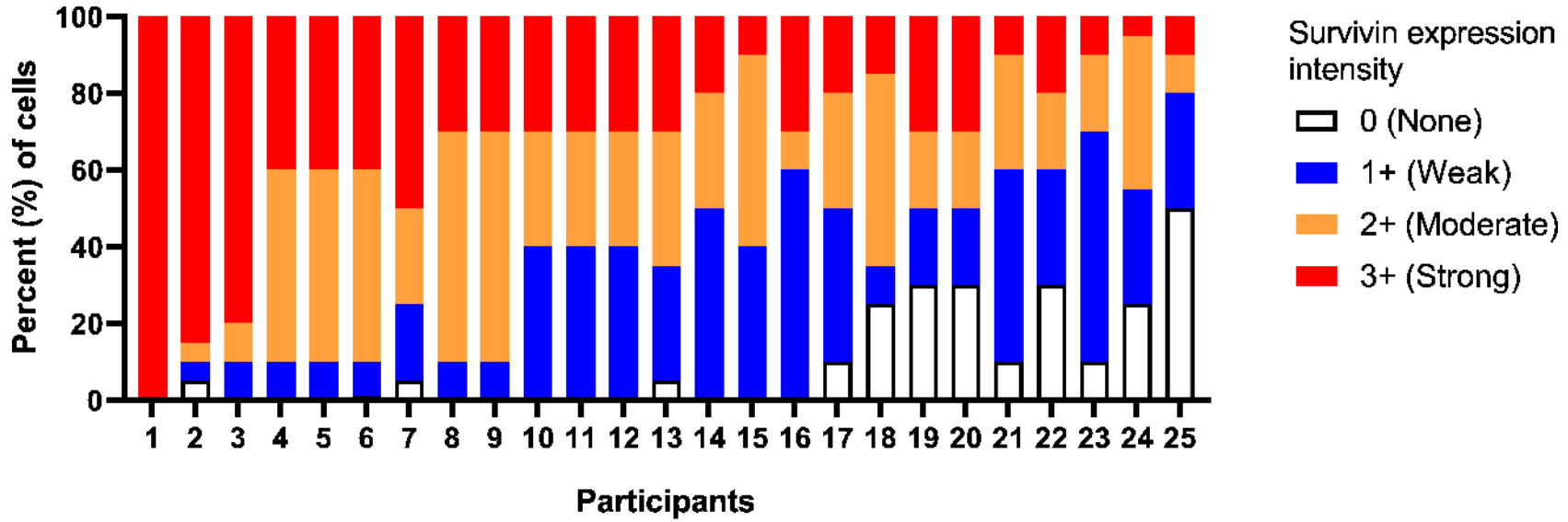

Figure 1. Heterogeneity of survivin intensity expression in pre-treatment tumour biopsies from participants with R/R DLBCL undergoing treatment in SPiReL clinical trial

Figure 1