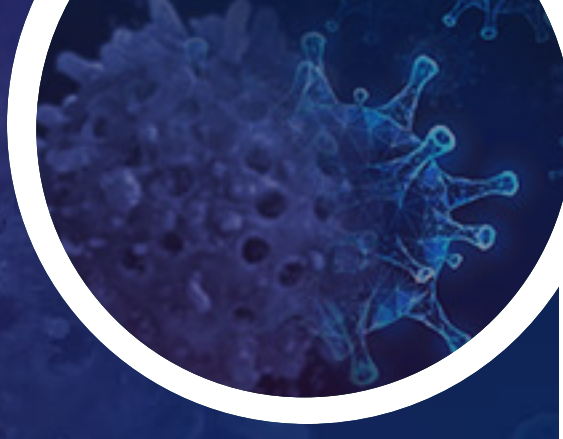
ASH 2021

Tapping the Immune Microenvironment in B-cell Lymphomas



B-cell lymphomas constitute ~80% of the non-Hodgkin lymphomas and the classification is based on tumor cell morphology, immune phenotype, and genetic alterations.

The features and composition of the tumor microenvironment (TME) differ among the types of lymphoma. Immune cells in the TME of diffuse large B-cell lymphoma (DLBCL) include natural killer (NK) cells (+/−20% of total cell content), dendritic cells (DCs) (+/−15%), M2-type macrophages (+/−15%), CD4+ T cells (+/−10%), and CD8+ T cells (< 5%). Whereas, the TME of CLL is complex and multidimensional. Monocytes, macrophages and T cells are the immune cells most commonly found in very variable frequencies.[1,2]

Increasing knowledge of the TME composition and complex interactions between tumor cells and surrounding immune cells has triggered the development of drugs that target these mechanisms.

ASH 2021 highlights potential new targets that are being studied as a promising immunomodulatory therapeutic strategy in B-cell lymphomas

CD27

This belongs to the tumor necrosis factor receptor superfamily (TNFRSF) and acts as a co-stimulatory molecule, enhancing T- and B-cell responses. The CD27 agonist antibody, varlilumab, induced CD4+ and CD8+ T-cell effector and memory activation in B-cell lymphoma patients. It is being studied in combination with rituximab (CD20 mAb) which leads to tumor cell killing by antibody-directed cellular cytotoxicity and/or phagocytosis (ADCC/ADCP). ***(Phase II RiVa study-NCT03307746) (Celldex Therapeutics)***[3]

CD47

CD47 blockade mainly inhibits the CD47-SIRPα axis to prevent tumor immune escape. ***IBI-188 (letaplimab) binds*** to CD47, a surface protein that provides a “don’t eat me” signal to macrophages. While binding to the CD47 antigen on the surface of tumor cells, it blocks the CD47-SIRPα signaling pathway, and promotes the phagocytosis of tumor cells by macrophages, thereby exerting an anti-tumor effect. A study in DLBCL tissue samples is exploring association with anti-CD47 response. ***(Innovent Biologics)***[4]

Additionally, selected abstracts also provide insights on the differential effects of approved targeted therapies on different signaling pathways in ***various immune cell subsets.***

Gene expression analysis of BTK inhibitor (BTKi) treated mantle cell lymphoma (MCL) patient tissue samples revealed distinct tumor microenvironment-associated signatures which were identified as normal lymph node like, immune cell-enriched, mesenchymal, and immune depleted or deserted. BTKi-resistant MCL primarily exhibited immune-depleted TME subtype. Somatic mutations TP53, NSD2, NOTCH1, KMT2D, SMARCA4, which were previously reported in ibrutinib-resistant MCL and/or in refractory high-risk MCL patients, were predominant in the immune-depleted TME cluster.[5]

Gene profiling of rituximab treated follicular lymphoma (FL) patient samples confirmed specific immune signatures to be a powerful outcome predictor and defined a subset of FL patients obtaining maximal benefit from frontline rituximab. The results indicate that patients with a favorable immune signature could derive maximal benefit from a first-line chemo-free treatment approach with single-agent rituximab.[6]

References

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SmartAnalyst will focus on the key presentations to help clients understand the tumor immune landscape and its impact in B-Cell lymphoma treatment.

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