Mechanism-driven Combination Targeted Therapies for Diffuse Large B-cell Lymphoma

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Diffuse large B cell lymphoma (DLBCL) is a heterogenous set of aggressive cancers comprised of 3 gene expression subtypes that have been further subdivided into 7 related genetic subtypes. The extraordinary molecular diversity of DLBCL presents a significant clinical challenge since each molecular subtype responds differentially to chemotherapy and targeted therapies. Functional genomic and chemical screens uncovered multiple oncogenic pathways that are essential for the survival in these lymphomas, some that are restricted to particular subtypes and others that shared. Monotherapy with drugs targeting these pathways produces objective but rarely durable remissions. Drugs targeting parallel oncogenic survival mechanisms are frequently synergistic, providing a foundation for the development of multidrug regimens that induce cell death by blocking several survival pathways simultaneously. In this presentation, I will review our current understanding of the targetable oncogenic mechanisms in subtypes of DLBCL, which will focus on inhibition of B-cell receptor signaling and anti-apoptosis. I will show how we have harnessed this knowledge to rationally develop and test a therapeutic regimen composed of 5 to 6 targeted agents, termed ViPOR-(polatuzumab), which produced durable remissions in patients with relapsed/refractory DLBCL without the need for maintenance therapy or consolidation. ViPOR had high activity in non-GCB DLBCL, with CRs in 62% of patients and a 2-year PFS of 39%. Consistent with previous pre-clinical and clinical findings, the MCD subtype was significantly more responsive to ViPOR than other subtypes (83% CR. Quite unexpectedly, ViPOR induced CRs in 53% EZB-DH cases, yielding a 2-year PFS of 47%. Given the durable remissions and likely cures attained with ViPOR therapy, a multi-center phase II study is ongoing (NCT06649812), enrolling patients with relapsed/refractory non-GCB and EZB-DH DLBCL. The development of ViPOR suggests how these design principles form a novel paradigm for the development of potentially curative targeted therapy.