Rational development of targeted therapies to cure molecular subtypes of DLBCL

Louis M. Staudt

National Cancer Institute, USA

Chronic active B cell receptor (BCR) signaling is a key survival pathway in diffuse large B cell lymphoma (DLBCL), particularly in the ABC gene expression subgroup. The BTK kinase inhibitor ibrutinib kills ABC DLBCL cells by blocking this pathway and decreasing downstream NF- B activation. A phase II trial of ibrutinib monotherapy in relapsed/refractory DLBCL demonstrated frequent responses in the ABC but not GCB subgroup. This prompted a phase III trial (“Phoenix”) in previously untreated patients with non-GCB DLBCL testing the effect of adding ibrutinib to R-CHOP chemotherapy. Younger patients (age<60) had significantly improved progression-free and overall survival when receiving ibrutinib, but the molecular basis for this benefit is unknown. Recent multi-platform genetic profiling revealed a genetic taxonomy of DLBCL that subdivides the ABC subgroup into 4 genetic subtypes that are characterized by recurrent genetic aberrations, distinctive gene expression signatures, and differential responses to R-CHOP chemotherapy. The exceptional benefit of ibrutinib in particular DLBCL genetic subtypes will be discussed. Beyond chemotherapy, we are developing potentially curative therapies for lymphomas by combining targeted agents that block key survival pathways in the malignant cells. Recent progress in developing a therapeutic regimen combining 5 targeted agents will also be discussed.