

B-cell non Hodgkin lymphomas (B-NHL) represent the most common subgroup of hematologic malignancies. Diffuse large B-cell lymphoma (DLBCL) represents the most frequent type of B-NHL in the Western hemisphere. DLBCL belongs to aggressive lymphomas, which usually require urgent initiation of therapy with combined immunochemotherapy regimen. Despite improvement of prognosis of DLBCL patients in recent two decades substantial part of patients either do not respond to therapy or undergo early relapse of the lymphoma. Prognosis of relapsed / refractory (R/R-) DLBCL is dismal and requires development and testing of novel anti-lymphoma agents. Better understanding of the biology of DLBCL is a key factor for successful design of novel drugable molecules. DLBCL harbors defects in many key molecules involved in the regulation of apoptosis, which increases lymphoma chemoresistance. In the manuscript by Klanova et al published recently in the Clinical Cancer Research we have demonstrated a novel division of DLBCL according to the respective dependence of lymphoma cells on the key anti-apoptotic regulators BCL2 and MCL1. In brief, we have brought evidence of existence of two broad subgroups of DLBCL: 1. BCL2-dependent, and 2. MCL1-dependent. BCL2-dependent DLBCL are highly sensitive to BCL2-specific inhibitor ABT-199, but are resistant to MCL1-targeting agent homoharringtonine (HHT), while MCL1-dependent DLBCL demonstrate the opposite sensitivities. These findings were confirmed by detailed analysis of apoptotic signaling in both defined lymphoma subgroups. Using murine models of BCL2-positive R/R-DLBCL developed in our laboratory we have confirmed strong anti-lymphoma synergism between ABT-199 and HHT (Figure 1). The results of our study will impact design of future treatment strategies in DLBCL.

Klanova M, Andera L, Brazina J, Svadlenka J, Benesova S, Soukup J, Prukova D, Vejmelkova D, Jaksá R, Helman K, Vockova P, Lateckova L, Molinsky J, Maswabi BC, Alam M, Kodet R, Pytlík R, Trněný M, Klener P. Targeting of BCL2 Family Proteins with ABT-199 and Homoharringtonine Reveals BCL2- and MCL1-Dependent Subgroups of Diffuse Large B-Cell Lymphoma. Clin Cancer Res. 2016 Mar 1;22(5):1138-49. PMID: [26467384](https://pubmed.ncbi.nlm.nih.gov/26467384/).