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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

CDCA2 Is a Predictive Marker and Mediator of Bortezomib Response in Diffuse Large B-Cell Lymphoma

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Objective: In recent years randomized phase III clinical trials have attempted to improve first-line R-CHOP treatment of diffuse large B-cell lymphoma (DLBCL) through addition or substitution of drugs. Bortezomib treatment has shown significant clinical efficacy in other B-cell malignancies, and the REMoDL-B trial testing R-CHOP vs. RB-CHOP in DLBCL patients stratified by cell of origin revealed at 60 months follow-up that ABC and molecular high-grade patients significantly benefitted in clinical outcome. This study aims at identifying predictive markers of bortezomib response combined with functional investigation of their biological impact in DLBCL irrespective of molecular subtypes.
Methods: Data from the REMoDL-B trial including 450 patients in each treatment arm was retrospectively analyzed. We fitted a multivariate Cox regression model testing all expressed genes with overall survival as outcome and an interaction term between gene expression and treatment arms (R-CHOP and RB-CHOP) as covariates, including their main effects. For the top candidate, CDCA2, survival was visualized using Kaplan-Meier analysis of patients stratified by median expression. Functional examination of CDCA2 was performed by applying CRISPR/Cas9 genome editing. Knockout of *CDCA2* was conducted in two DLBCL cell lines, representing ABC and GCB cell of origin, and effect on proliferation, cell cycle distribution, and drug response was examined in MTS-assays and by flow cytometry. A DLBCL xenograft mouse model was established with *CDCA2* knockout and control DLBCL cells, respectively, and time to tumor formation and death was monitored and tumors molecularly characterized.
Results: DLBCL patients with high expression of CDCA2 have superior outcome when treated with RB-CHOP in comparison to R-CHOP (p=0.0097), whereas no difference in outcome was observed for patients with low CDCA2 expression (p=0.086) (Figure 1), supporting high expression of CDCA2 as a predictive marker of bortezomib response irrespective of cell of origin subclassification. Knockout of *CDCA2* decreased DLBCL cell proliferation rate and affected the cell cycle transition between the G1 and S-phase, resulting in an increased percentage of cells in G1 compared to the scramble control. Bortezomib dose-response analysis revealed reduced sensitivity in *CDCA2* knockout cells compared to the control (Figure 2A). In addition, *CDCA2* knockout cells were also less sensitive to carfilzomib, a 2 nd generation proteasome inhibitor. In combinatory drug experiments comparing CHOP and B-CHOP, *CDCA2* knockout cells demonstrated higher relative resistance compared to controls cells when exposed to B-CHOP than CHOP (Figure 2B+C), illustrating CDCA2 to be cardinal and specifically mediating the bortezomib response. In DLBCL xenograft models, *CDCA2* knockout tumors displayed reduced growth rate in comparison to control tumors. Due to the substantial tumor burden, control DLBCL xenografted mice had shorter survival time than *CDCA2* knockout DLBCL mice (Figure 2D).
Conclusion: DLBCL patients with high expression levels of CDCA2 benefitted the most from addition of bortezomib to R-CHOP. In functional studies, the loss of *CDCA2* increased cellular resistance to bortezomib in both single- and combinational drug studies.

Disclosures No relevant conflicts of interest to declare.

Figure 1

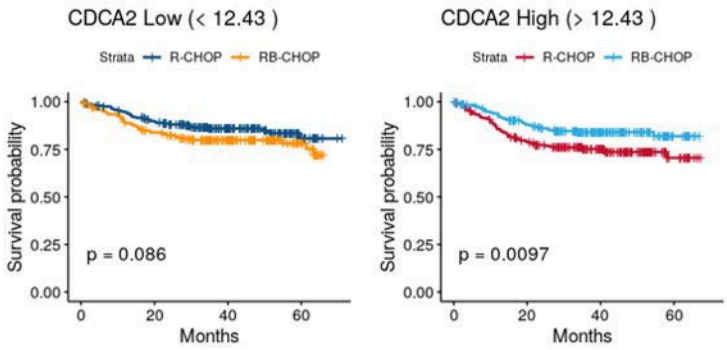

Figure 2

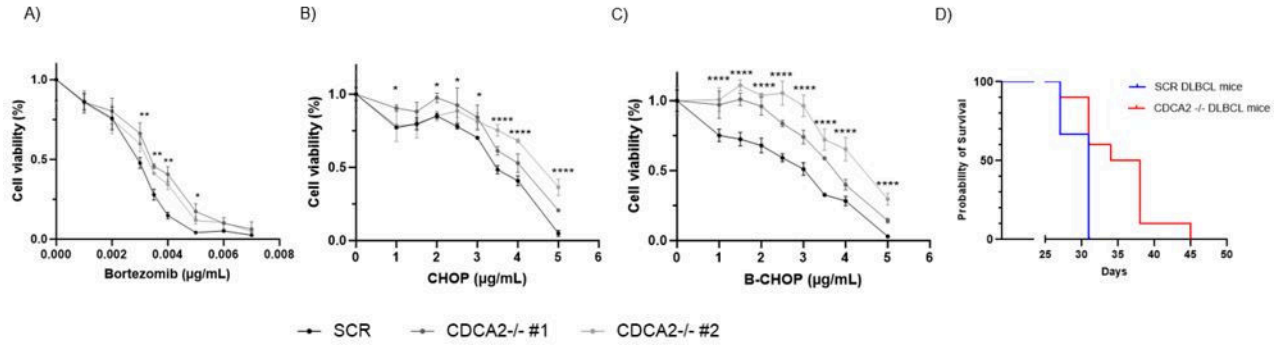

Figure 1

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