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Therapeutic potential of polatuzumab vedotin for the treatment of diffuse large B-cell lymphoma

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is typically treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Although most patients can be cured with R-CHOP, up to one-third of them relapse with a dismal outcome in most cases. Numerous approaches have been attempted to improve the therapeutic outcomes in DLBCL patients.

Polatuzumab vedotin is an antibody–drug conjugate (ADC) targeting CD79b, which is ubiquitously expressed on over 90% of B-cell NHL malignancies, including DLBCL. To determine the potential of polatuzumab vedotin as a therapeutic agent, we evaluate its potency across a series of DLBCL patient derived xenograft (PDX) models.

Method

We established and characterized a series of DLBCL lymphoma PDX models. Eight DLBCL PDX models were selected for polatuzumab vedotin efficacy study, of which three are GCB DLBCL. Gene expression pattern analysis of these lymphoma PDX models was performed using an Illumina NovaSeq 6000 system following Illumina-provided protocols for 2x150 paired-end sequencing. The expression status of CD79b on these DLBCL PDX models was also evaluated by IHC.

Results

Table 1 Clinical information, CD79b expression and IHC score of the DLBCL lymphoma PDX models.

The gene expression level (FPKM) was quantified by RSEM

Model ID	Cancer type	Pathological Diagnosis	Subtype	CD79B Expression	CD79B IHC H-score
LY-24-0016	Lymphoma	DLBCL	Non-GCB	678.45	240
LY-24-0063	Lymphoma	DLBCL	Non-GCB	759.01	218
LY-24-0169	Lymphoma	DLBCL	Non-GCB	818.26	235
LY-24-0207	Lymphoma	DLBCL	GCB	1466.66	224
LY-24-0236	Lymphoma	DLBCL	Non-GCB	537.48	195
LY-24-0395	Lymphoma	DLBCL	GCB	773.41	205
LY-24-0398	Lymphoma	DLBCL	GCB	1122.11	272
LY-24-0402	Lymphoma	DLBCL	Non-GCB	531.36	288

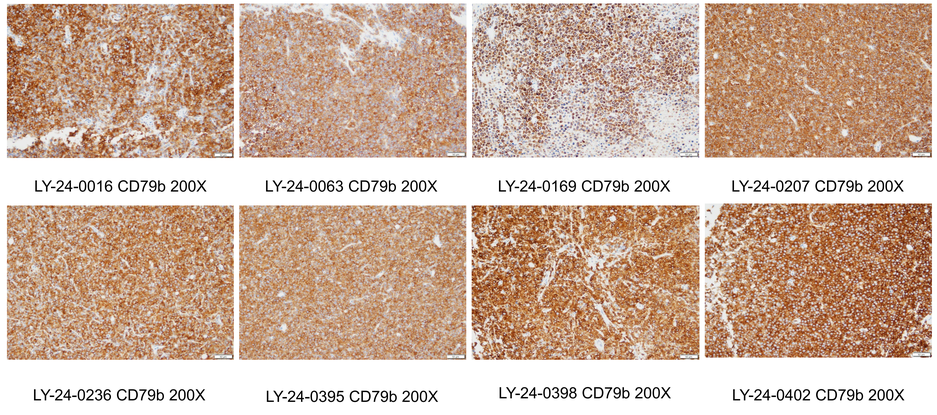

Fig.1 Immunohistochemically staining of CD79b in DLBCL lymphoma PDX models.

Tumor tissues were stained using anti-CD79b (CST, 96024, 1:100) monoclonal antibodies. All lymphoma PDX models are positive for CD79b. Scale bar = 50 μm.

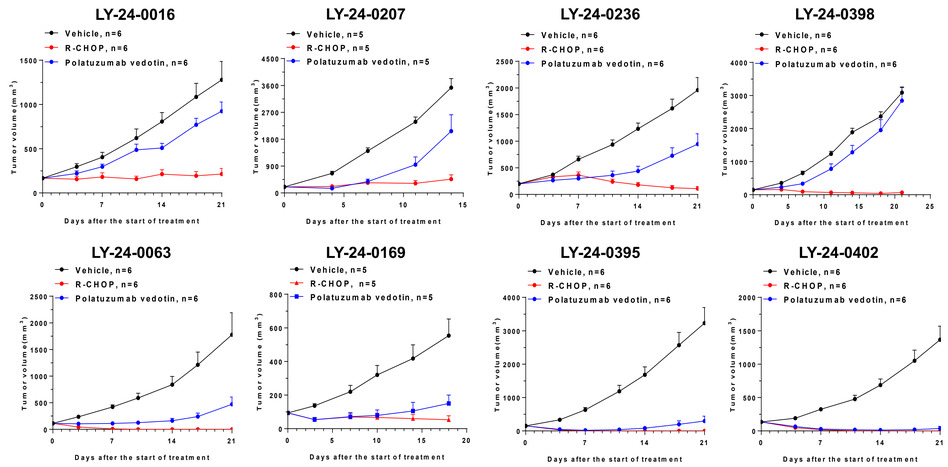

Fig.2 The response of Polatuzumab vedotin in DLBCL lymphoma PDX models.

NOD-SCID mice were implanted subcutaneously at the right flank for model development. When the tumor volume reached appropriate size, the mice were randomly divided into three groups according to tumor volume and body weight. The data are presented as means ± SEM.

For the xenograft experiment, polatuzumab vedotin was dosed once intravenously at 2 mg/kg. Rituximab was dosed twice a week at 10 mg/kg intraperitoneally. CHOP (intraperitoneal injection of 30 mg/kg cyclophosphamide, 2.475 mg/kg doxorubicin, 0.375 mg/kg vincristine, and oral dosing of 0.15 mg/kg prednisone once a day for 5 days) was dosed in combined with rituximab.

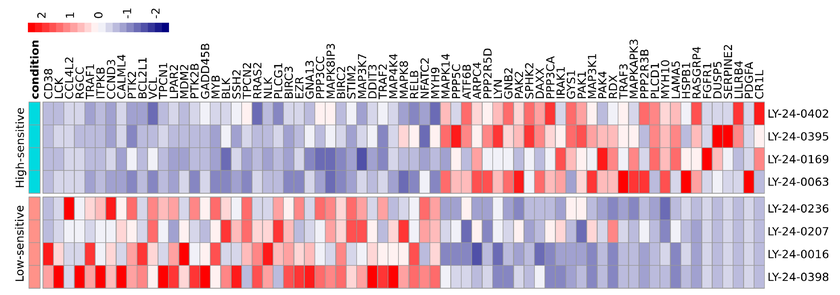

Fig.3 Biomarker analysis of lymphoma PDX treated with polatuzumab vedotin.

Expression data were grouped into two group according to their sensitivity to polatuzumab vedotin, highly sensitive group and low sensitive group. Transcriptome differential expression (DE) analysis was performed by using edgeR. Genes with Pvalue<0.05, log2FC>0.5 or log2FC <-0.5 were regarded as differential genes.

Conclusion

- Our results show that a single dose of polatuzumab vedotin at just 2 mg/kg could reach a comparable effect with R-CHOP and no significant body weight loss was observed. Among the 8 lymphoma PDX models tested, 50% of them are sensitive to polatuzumab vedotin treatment.
- Our results show that there is no apparent correlation between polatuzumab vedotin responses and CD79b expression (IHC Score).
- 69 differential expression genes were observed in canonical resistance pathway after polatuzumab vedotin treatment, including B cell receptor signaling pathway, bypass MAPK, PI3K-AKT, NF-kb, calcium signaling pathway. The expression level of Bcl-xL (BCL2L1) has been reported to correlate with reduced sensitivity to anti–CD79b ADC. Our results also show that in the drug low-sensitive group, BCL2L1 was highly expressed, revealing that BCL2L1 may be an important biological marker with therapeutic potential of polatuzumab vedotin. Further investigation is in progress.

References

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