

# Continuing Medical Education



Follow-Up VISIT from PER®



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### Disclosures

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# 3 Things You Should Know About Biomarkers in DLBCL

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## LEARNING OBJECTIVES

*Upon successful completion of this activity, you should be better prepared to:*

- Identify current and emerging biomarkers that can inform clinical decision-making in patients with DLBCL
- Describe how results of biomarker testing can be used to determine targeted treatments for patients with DLBCL

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**D**iffuse large-B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, comprising up to 40% of all newly diagnosed cases.<sup>1</sup> DLBCL is a genetically heterogeneous malignancy with multiple subtypes and recent investigations based on molecular profiles have opened the possibility for personalized therapy in this disease space. Here are 3 things you should know about the use of biomarkers in DLBCL.

## 1 Biological heterogeneity appears to drive outcomes associated with standard treatment.

The 2 largest cell-of-origin (COO) subtypes arising from different stages of lymphoid differentiation, activated B cell (ABC) and germinal center B cell (GCB), comprise 50% and 30% of DLBCL cases, respectively.<sup>1</sup> Although combination rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy is curative in approximately 60% of patients, those who do not respond to R-CHOP often have dismal outcomes.<sup>2</sup> Patients with the ABC subtype tend to be among those who experience poor outcomes, with a 3-year progression-free survival (PFS) following R-CHOP of 40% vs 75% in patients with GCB DLBCL ( $P < .001$ ).<sup>3</sup>

Timely identification of patients' COO subtypes can enable the creation of individualized treatment plans to promote optimal patient outcomes. With that goal in mind, the Lymphoma/Leukemia Molecular Profiling Project developed the Lymph2Cx assay, a digital gene expression (NanoString)-based test to assign COO using immunohistochemistry on formalin-fixed paraffin-embedded tissue.<sup>4</sup> This protocol uses less expensive tests on more readily available material than previous assays. Validation of the Lymph2Cx assay against the gold-standard gene expression profiling methods using a cohort of 20 genes resulted in Lymph2Cx correctly designating 57 of 58 cases (98%) as ABC, GCB, or unclassified (5%-7% of cases). COO classification using the Lymph2Cx method correlated strongly with patient outcomes. Patients with ABC DLBCL were more likely to experience disease progression than those with the GCB subtype (relative risk [RR], 3.6; 95% CI, 1.6-8.4;  $P < .001$ ). When the same participants were classified according to the gold standard, the correlation was less strong (RR, 2.6; 95% CI, 1.1-6.3;  $P = .01$ ).

Although the ABC and GCB subtypes share some targetable oncogenic pathways, they each also have unique genetic alterations that might indicate better efficacy of a drug in one subtype over the other (Figure).<sup>2</sup> In a subgroup analysis of the phase 3 POLARIX trial (NCT03274492), the antibody-drug conjugate (ADC) polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) yielded better outcomes vs R-CHOP in patients with ABC DLBCL but not in patients with GCB DLBCL.<sup>5,6</sup> In the overall population, the 2-year PFS rate was

76.7% (95% CI, 72.7%-80.8%) with pola-R-CHP vs 70.2% (95% CI, 65.8%-74.6%) with R-CHOP.<sup>5</sup> However, the HR for disease progression, relapse, or death for pola-R-CHP vs R-CHOP was 0.34 (95% CI, 0.13-0.85) in the ABC subgroup vs 1.18 (95% CI, 0.75-1.84) in the GCB subgroup.<sup>6</sup> Although the safety profiles of the 2 regimens were generally similar, the incidence of febrile neutropenia was higher among patients receiving pola-R-CHP vs R-CHOP (13.8% vs 8.0%). Therefore, R-CHOP might be the preferred regimen for patients with GCB DLBCL who appear to receive no benefit from pola-R-CHP.

## 2 Outcomes of patients with double-hit DLBCL are worse than for those with a single MYC or BCL2 aberration.

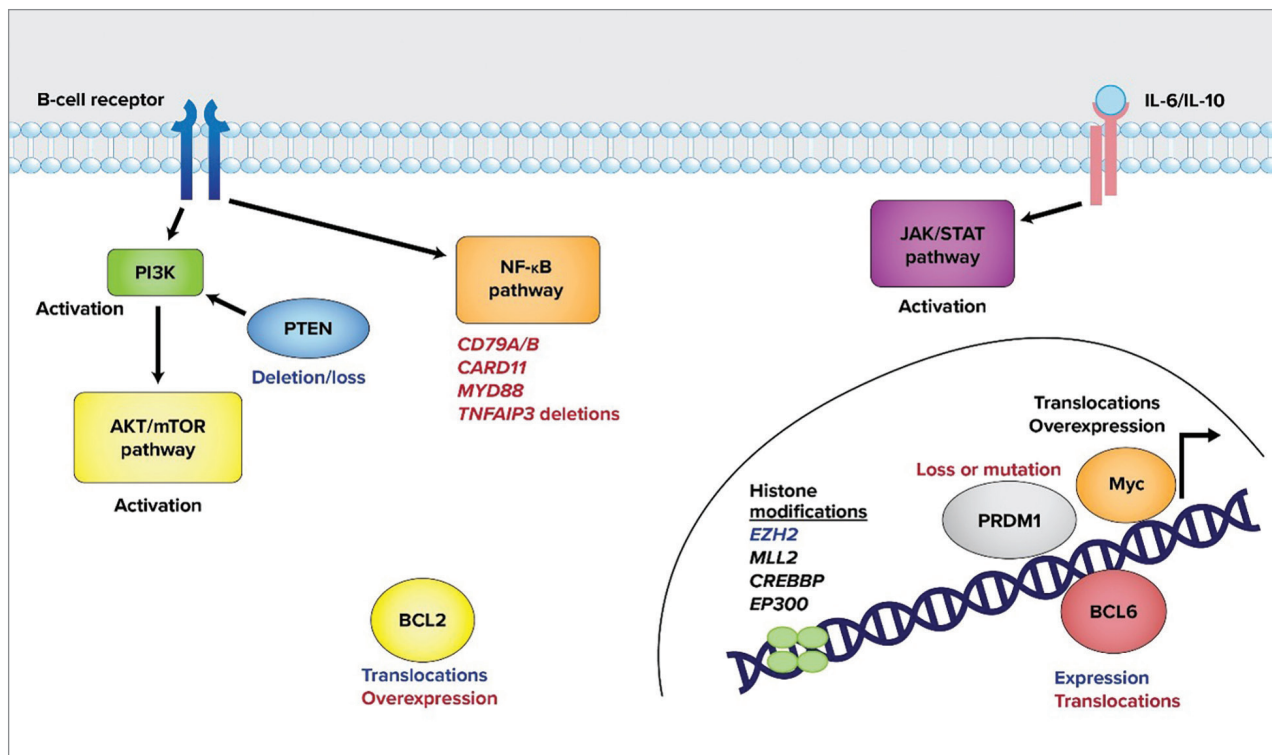
A minority of patients with DLBCL (10%) harbor both *MYC* gene rearrangements, and approximately half of them also harbor rearrangements in *BCL2*, *BCL6*, or both, conditions termed double-hit DLBCL (DHL) and triple-hit DLBCL (THL), respectively.<sup>1</sup> These cases arise largely in the GCB subtype. Multiple retrospective studies suggest that patients with DHL have poorer outcomes with standard therapy. One analysis of 167 patients with DLBCL demonstrated that, relative to the overall population, those with DHL had reduced overall survival (OS) (HR, 3.2;  $P = .001$ ).<sup>7</sup>

Higher-intensity chemoimmunotherapy may provide better outcomes than R-CHOP for patients with DHL. A single-arm, phase 2 study (NCT01092182) enrolled 53 patients with DLBCL, including 19 with *MYC* rearrangements and 24 with DHL to receive dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R).<sup>8</sup> The 48-month event-free survival (EFS) was 71.0% (95% CI, 56.5%-81.4%), and the 48-month OS was 76.7% (95% CI, 62.6%-86.1%). Grade 4 adverse events included neutropenia (53%) and thrombocytopenia (13%). Febrile neutropenia of any grade was reported in 19% of patients. Treatment-related death due to infection occurred in 3 patients. As a result of this study, DA-EPOCH-R became the preferred treatment for patients with DHL.

A subsequent retrospective study of 6412 patients with DLBCL, including 304 with DHL or THL, demonstrated that patients with DHL/THL who received R-EPOCH as first-line treatment ( $n=131$ ) had significantly improved OS (median not reached [NR]) vs those who received R-CHOP in the first line ( $n=97$ ; median OS, 20.2 months; 95% CI, 14.8 months to NR).<sup>9</sup> Treatment with R-EPOCH resulted in a 50% lower risk of death (HR, 0.50; 95% CI, 0.33-0.77). There were no significant survival benefits for either regimen in patients without DHL/THL.

Based on the presence of *BCL2* rearrangements in patients with DHL, the Alliance A051701 phase 2/3 study (NCT03984448) investigated the benefit of adding venetoclax to DA-EPOCH-R.<sup>10</sup> There was no benefit to response rates, PFS, or OS with the

**FIGURE. Common Signaling Pathway Alterations in DLBCL<sup>2</sup>**



ABC, activated B cell; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell.

Alterations shown in black are found in all types of DLBCL. Alterations shown in blue are more common to GCB DLBCL. Alterations shown in red are more common to ABC DLBCL.

addition of venetoclax compared with patients receiving only DA-EPOCH-R. Furthermore, 6 patients (17%) receiving venetoclax plus DA-EPOCH-R died during treatment due to sepsis (n=4) or cardiac arrest (n=2) vs 1 patient (3%) in the DA-EPOCH-R-only arm (due to *Pneumocystis jirovecii* pneumonia).

An alternative drug combination of cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate with ifosfamide, etoposide, high-dose cytarabine and rituximab (CODOX-M/IVAC-R) was compared with DA-EPOCH-R in a retrospective analysis of 113 patients younger than 60 years who had DHL/THL.<sup>11</sup> Complete response was achieved by 80% of the 49 patients receiving CODOX-M/IVAC-R vs 58% of the 64 patients receiving DA-EPOCH-R. Additionally, treatment with CODOX-M/IVAC-R was associated with improved EFS vs DA-EPOCH-R (HR, 0.54; 95% CI, 0.31-0.97). However, there was no OS benefit.

### 3 ADCs may represent new options for patients with R/R DLBCL.

Outcomes tend to be dismal for patients with relapsed/refractory (R/R) DLBCL. The ECHOLON-3 trial (NCT04404283)

investigated whether adding the anti-CD30 ADC brentuximab vedotin (BV) to lenalidomide plus rituximab (R<sup>2</sup>) could improve outcomes for patients with R/R DLBCL who were ineligible for transplant or chimeric antigen receptor (CAR) T-cell therapy.<sup>12</sup> Results are outlined in the **Table**.<sup>12</sup> Benefit with BV plus R<sup>2</sup> was even seen in patients without high expression of CD30.

The search is ongoing for a curative therapy for patients who do not respond to R-CHOP; however, outcomes are steadily improving with novel therapy combinations. ■

#### KEY REFERENCES

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**TABLE. Addition of Brentuximab Vedotin to Lenalidomide and Rituximab in R/R DLBCL<sup>12</sup>**

OVERALL	ORR, % (95% CI)	CR, %	MEDIAN OS, MO (95% CI)	MEDIAN PFS, MO (95% CI)
<b>BV + R<sup>2</sup></b>	64.3 (54.7%-73.1%)	40.2	13.8 (10.3-18.8)	4.2 (2.9-7.1)
<b>Placebo + R<sup>2</sup></b>	41.5 (32.5%-51.0%)	18.6	8.5 (5.4-11.7)	2.6 (1.4-3.1)
<b>HR (95% CI)</b>	<i>P</i> = .0006	-	0.629 (0.446-0.891) <i>P</i> = .0085	0.527 (0.380-0.729) <i>P</i> < .0001

**BV + R<sup>2</sup> Subgroups**

<b>CD30+</b>	72.2	38.9	-	-
<b>CD30-</b>	60.5	40.8	-	-

BV, brentuximab vedotin; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R<sup>2</sup>, lenalidomide plus rituximab; R/R, relapsed/refractory.

**1 In studies investigating polatuzumab vedotin plus R-CHP versus R-CHOP alone for newly diagnosed or relapsed/refractory DLBCL, which cell of origin subtype appears to benefit most in terms of PFS from polatuzumab vedotin?**

- A. Activated B-cell like only
- B. Germinal center B-cell like only
- C. Both activated B-cell like and germinal center B-cell like

**2 In the phase 3 ECHELON-3 study, what was the apparent impact of CD30 positivity overall survival with the addition of brentuximab vedotin to lenalidomide plus rituximab for patients with relapsed/refractory DLBCL?**

- A. There was no clear difference in survival.
- B. CD30+ disease was associated with longer survival than CD30- disease.
- C. CD30- disease was associated with longer survival than CD30+ disease.

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