Evaluation of Gene Expression Assays to Classify Large B-Cell Lymphoma by Molecular Subtype from Formalin Fixed Paraffin Embedded Tumor Biopsy Tissue (FFPET)

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Introduction

- Gene expression profiling (GEP)-based classification of large B-cell lymphoma (LBCL) into molecular subtypes such as activated B-cell-like (ABC), dark-zone signature (DZsig), and other germinal center B-cell-like (GCB), can provide prognostic information and guide frontline treatment decisions.

Aim

To create a clinical grade reporting system for cell-of-origin (COO) and DZsig classification by comparing the concordance of GEP using the Nanostring DLBCL90 assay (DLBCL90) and whole transcriptome sequencing (WTS) using the BostonGene Tumor Portrait™ test and the gneSeqCOO algorithm modified to classify tumors into ABC, GCB, and DZsig+ subtypes.

Methods

- A total of 119 FFPET samples from 113 patients receiving care at MD Anderson Cancer Center (MDACC) underwent WTS analysis at BostonGene (BG)[1] and the Nanostring DLBCL90[2] assay at MDACC to define COO and DZsig status.
- Transcriptomic data were profiled to define COO using the gneSeqCOO method[3] and DZsig using a novel method (gneSeqDZsig).
- COO and DZsig status were evaluated for concordance between these methods. Only tumors with GCB/UNCLASS COO were compared for DZsig concordance.
- This cohort was enriched for tumors with *MYC* and *BCL2* rearrangements (DH-*BCL2*; likely to be DZsig+) to support validation across the range of scores.

Results

- The median age was 61 years; most patients were male and of white race. The most common frontline treatments were R-CHOP (47%) and R-EPOCH (26%). In this cohort, 20 (18%) patients had tumors identified as *DH-BCL2* by FISH. (Table 1)
- The correlation between DLBCL90 COO and gneSeqCOO linear prediction score (LPS) scores was 0.97 (P < 0.0001), with an overall classification concordance of 0.86 (95% confidence interval [CI] 0.78 - 0.92). (Figure 1)
- The correlation between DLBCL90 DZsig and gneSeqDZsig LPS scores was 0.96 (P < 0.0001), with an overall score concordance of 0.85 (95% CI 0.74-0.93) and 0% frank class discordance. (Figure 2)

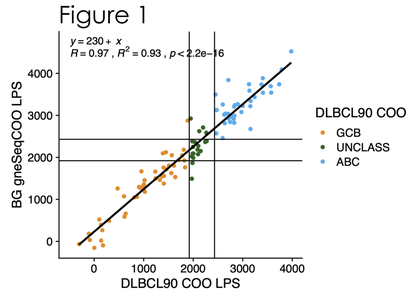
Results

- Among 75 samples classified as ABC or GCB by both DLBCL90 and gneSeqCOO, 1 (1.3%) was frankly discordant.
- For patients with previously untreated disease, those with DZsig+ tumors had significantly inferior 2-year PFS and OS compared to patients with ABC and GCB tumors. (Table 2)

Table 1: Patient characteristics

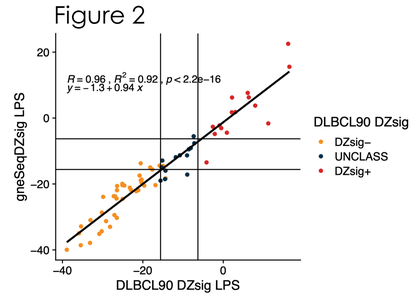
	Overall Cohort (N=113)
Age (at diagnosis)	
Median	61
Range	15-85
Male Sex	68
Race	
White	78
Black or African American	4
Asian	9
Other	15
Not Reported	7
Ethnicity	
Hispanic	15
Non-Hispanic	72
Unknown	26
FISH (*MYC, BCL2, BCL6*)	
DHIT+ (*MYC+BCL2+*)	13
THIT+ (*MYC+ BCL2+ BCL6+*)	7
DHIT-	53
Unknown	40
Line of Treatment	
Frontline	68
Relapsed	44
Unknown	1
Treatment (frontline)	
R-CHOP	32
R-EPOCH	18
R-hyperCVAD	2
Other	16

Figure 1



Correlation between DLBCL90 COO and WTS gneSeqCOO LPS scores for COO classification. Horizontal and vertical black lines represent the thresholds for ABC and GCB classifications.

Figure 2



Correlation between DLBCL90 DZsig and WTS gneSeqDZsig scores for DZsig classification. Horizontal and vertical black lines represent the thresholds for DZsig+ and DZsig-IND classifications. Only tumors classified as GCB or UNCLASS by DLBCL90 COO are shown.

Table 2: Patient Outcomes by COO and DZsig Status as determined by DLBCL90 or WTS using the gneSeqCOO/DZsig algorithms

		ABC	GCB	DZsig+	p-value (log rank)
CRR	DLBCL90	63%	63%	11%	
	WTS	75%	56%	17%	
ORR	DLBCL90	63%	75%	33%	
	WTS	75%	69%	38%	
2-year PFS	DLBCL90	49.3%	80.6%	22.5%	.0124
	WTS	62.3%	82.5%	11.9%	.0015
2-year OS	DLBCL90	80.2%	90.8%	22.9%	.0003
	WTS	79.8.2%	84.8%	12.3%	.0003

CRR=complete response rate, ORR=overall response rate, PFS=progression free survival, OS=overall survival

Conclusions

These data demonstrate strong concordance between DLBCL90 and WTS-based assays for classifying COO and DZsig, defining another valid approach to identify molecular subgroups of LBCL.

References

1.Kotlov et al. Cancer Discov, 2021
2.Ennishi et al. JCO, 2019
3.Harris et al. Leuk Lymphoma 2025

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