BIOMARKER IDENTIFICATION IN RELAPSED/REFRACTORY NON-GERMINAL CENTER B-CELL–LIKE DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH ZANUBRUTINIB

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INTRODUCTION

- The non-germinal center B-cell–like (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL) is associated with poor clinical outcomes.[1]
- Zanubrutinib, a highly selective covalent Bruton's tyrosine kinase (BTK) inhibitor, was specifically engineered to decrease toxicities and improve tumor tissue distribution.[2]
- Inhibitors of BTK have established therapeutic activity in mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia and have shown modest activity in DLBCL.[3]
- Biomarker identification has gradually become the focus of DLBCL research.
- Here we report zanubrutinib efficacy and biomarker identification in relapsed/refractory (R/R) non-GCB DLBCL from four clinical studies.

METHODS

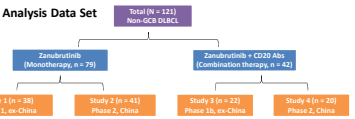
— 121 R/R DLBCL patients from 4 zanubrutinib studies were included in analysis

- 2 Monotherapy (zanubrutinib alone) studies and 2 Combination Therapy (Zanubrutinib plus anti-CD20 antibody) studies were included
- Similar eligibility criteria and response assessment criteria cross different studies
- Patients distribution and analysis data set shown in **Figure 1**

— Patient assessments

- Response: objective response rate (ORR) according to Lugano classification 2014
- GEP subtyping: performed by HTG EdgeSeq DLBCL Cell of Origin Assay using tumor FFPE samples collected before study drug treatment
- RNA-expression: gene expression readout by GEP subtyping assay were further analyzed by R package limma for correlation with response to zanubrutinib treatment
- DNA-sequencing: tumor FFPE samples were tested by next generation sequencing (NGS) and Chi-square test was used to evaluate the association between mutations and ORR

Figure 1. Analysis Data Set



	Monotherapy			Combination Therapy			
	Study 1 (n)	Study 2 (n)	Total (n)	Study 3 (n)	Study 4 (n)	Total (n)	Total (N)
Non-GCB DLBCL	38	41	79	22	20	42	121
ABC-DLBCL (GEP)	13	25	38	6	5	11	49
HTG GEP	15	29	44	7	5	12	56
DNA sequencing	10	34	44	15	18	33	77

Monotherapy: zanubrutinib
Combination Therapy: zanubrutinib + CD20 antibody
- Study 3: zanubrutinib + obinutuzumab
- Study 4: zanubrutinib + rituximab

RESULTS

- The unadjusted ORR in non-GCB DLBCL was similar across the four studies with an average of 30%. Median PFS of the four zanubrutinib studies ranged from 2.8m to 4.9m, and median OS ranged from 8.4m to 11.8m. (**Table 1**)

Table 1. Efficacy of Zanubrutinib in Non-GCB DLBCL

	Monotherapy			Combination Therapy			
	Study 1 (n=38)	Study 2 (n=41)	Total (n=79)	Study 3 (n=22)	Study 4 (n=20)	Total (n=42)	Total (N=121)
ORR, n (%)	12 (31.6)	12 (29.3)	24 (30.4)	5 (22.7)	7 (35.0)	12 (28.6)	36 (29.8)
95% CI [a]	(17.50, 48.65)	(16.13, 45.54)	(20.53, 41.75)	(7.82, 45.37)	(15.39, 59.22)	(15.72, 44.58)	(21.79, 38.74)
mPFS (Months) [b]	3.5	2.8	2.8	4.9	3.5	3.5	3.1
95% CI	(1.97, 5.52)	(2.56, 5.45)	(2.60, 4.80)	(1.71, 10.58)	(2.69, 5.55)	(2.69, 5.62)	(2.73, 4.93)
mOS (Months) [b]	11.8	8.4	8.8	11.8	10.3	11.6	9.9
95% CI	(5.09, 22.11)	(4.80, NE)	(5.52, 14.92)	(3.52, 16.53)	(5.39, NE)	(6.77, 15.21)	(6.80, 13.17)

Monotherapy: zanubrutinib
Combination Therapy: zanubrutinib + CD20 antibody
- Study 3: zanubrutinib + obinutuzumab
- Study 4: zanubrutinib + rituximab

ORR:Objective Response Rate
mPFS: median Progression-Free Survival
mOS: median Overall Survival
[a]: CI was calculated using the Clopper-Pearson method.
[b]: Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Data cut: Study 1 - September 9, 2019; Study 2 - August 31, 2019; Study 3 - August 31, 2019; Study 4 - May 31, 2019

- For 49 patients with GEP-confirmed activated B-cell (ABC) DLBCL classification, the ORR tended to be higher than non-GCB DLBCL although the number was small. The ORR was comparable for monotherapy (42%) and combination therapy (46%) for those with ABC-DLBCL(**Table 2**).

Table 2. Unadjusted ORR of Zanubrutinib in ABC-DLBCL

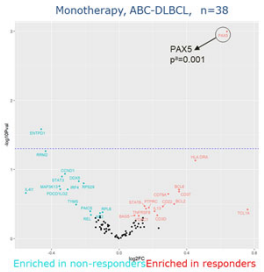
	Monotherapy			Combination Therapy			
	Study 1 (n=13)	Study 2 (n=25)	Total (n=38)	Study 3 (n=6)	Study 4 (n=5)	Total (n=11)	Total (N=49)
ORR, n (%)	7 (53.8)	9 (36.0)	16 (42.1)	3 (50.0)	2 (40.0)	5 (45.5)	21 (42.9)
95% CI	(25.13, 80.78)	(17.97, 57.48)	(26.31, 59.18)	(11.81, 88.19)	(5.27, 85.34)	(16.75, 76.62)	(28.82, 57.79)

Monotherapy: zanubrutinib
Combination Therapy: zanubrutinib + CD20 antibody
- Study 3: zanubrutinib + obinutuzumab
- Study 4: zanubrutinib + rituximab

ORR:Objective Response Rate
CI was calculated using the Clopper-Pearson method.
Data cut: Study 1 - September 9, 2019; Study 2 - August 31, 2019; Study 3 - August 31, 2019; Study 4 - May 31, 2019

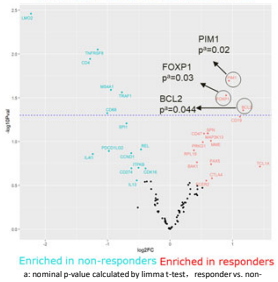
- For the 56 non-GCB patients with HTG gene expression profiles, PAX5 expression was higher in monotherapy responders than non-responders (**Figure 2A**), and PIM1, BCL2, and FOXP1 expression was higher in combination therapy responders than non-responders (**Figure 2B**).

Figure 2A. Genes Enrichment Analysis by Response to Zanubrutinib Monotherapy



a: nominal p-value calculated by limma t-test，responder vs. non-responder

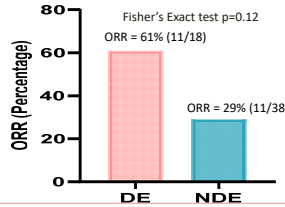
Figure 2B. Genes Enrichment Analysis by Response to Zanubrutinib Combination Therapy



a: nominal p-value calculated by limma t-test，responder vs. non-responder

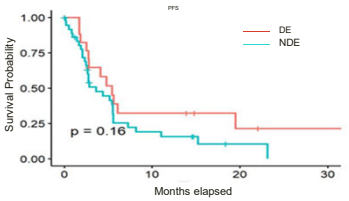
- Patients with MYC and BCL2 double-expressor DLBCL tended to have higher ORRs (11/18, 61% vs 11/38, 29%; P = 0.12) (Figure 3A) and longer progression-free survival (5.4 months vs 3.6 months; P = 0.16) (Figure 3B) and overall survival (10 months vs 7 months, P = 0.32) (Figure 3C).

Figure 3A. Correlation of BCL2/MYC Expression With Best of Response to Zanubrutinib



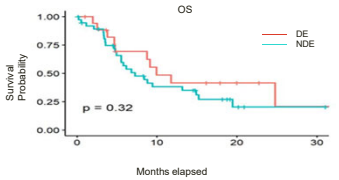
Median expression value of BCL2/MYC was used as threshold for defining BCL2/MYC high or low
DE: BCL2 and MYC double high expression by GEP
NDE: other than BCL2 and MYC double high expression by GEP

Figure 3B. Correlation of BCL2/MYC Expression With Progression-Free Survival



Median expression value of BCL2/MYC was used as threshold for defining BCL2/MYC high or low
DE: BCL2 and MYC double high expression by GEP
NDE: other than BCL2 and MYC double high expression by GEP

Figure 3C. Correlation of BCL2/MYC Expression With Overall Survival



Median expression value of BCL2/MYC was used as threshold for defining BCL2/MYC high or low
DE: BCL2 and MYC double high expression by GEP
NDE: other than BCL2 and MYC double high expression by GEP

- Patients with MYC and BCL2 double-expressor For the 77 patients with NGS panel data, non-GCB DLBCL with CD79B mutations (n = 25) showed significantly higher ORR than patients without CD79B mutations (n = 52) in the pooled analysis (60% vs 26.9%; P = 0.005). All three patients with NOTCH1 mutations responded to zanubrutinib monotherapy. The adjusted results showed a similar signal (**Table 3**).

Table 3. Correlation of CD79B/NOTCH1 Mutations With Response to Zanubrutinib

	Monotherapy (n = 44)	Combination Therapy (n = 33)	Total (N = 77)
CD79B			
CD79B[mut]	9/17 52.9	6/8 75.0	**15/25 60.0**
CD79B[WT]	9/27 33.3	5/25 20.0	**14/52 26.9**
Difference in ORR (95% CI) [a]	19.6 (-10.20, 46.87)	55.0 (15.75, 78.76)	**33.1 (9.60, 53.57)**
P-value [b]	0.1977	0.0041	**0.0050**
Adjusted P-value [c]			0.0104
NOTCH1			
NOTCH1[mut]	**3/3 100.0**	2/5 40.0	5/8 62.5
NOTCH1[WT]	**15/41 36.6**	9/28 32.1	24/69 34.8
Difference in ORR (95% CI) [a]	**63.4 (4.48, 76.54)**	7.9 (-27.98, 49.62)	27.7 (-6.78, 54.80)
P-value [b]	**0.0310**	0.7314	0.1256
Adjusted P-value [c]			0.0525

Monotherapy: zanubrutinib
Combination Therapy: zanubrutinib + CD20 antibody (obinutuzumab or rituximab)
[a] Difference 95% CI were based on Miettinen and Nurminen method.
[b] Chi-square test is used to compute p-value.
[c] Multivariate regression model is used to compute p-value with adjustment for baseline covariates and

CONCLUSIONS

- Zanubrutinib alone or in combination with an anti-CD20 antibody (obinutuzumab or rituximab) showed activity in the overall non-GCB DLBCL population.
- The retrospective biomarker analysis identified subsets of patients (such as PAX5 high or with CD79B mutations) with higher response rates to zanubrutinib treatment.

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