Biomarker Analysis of Zanubrutinib and Tislelizumab Combination Therapy in Patients With Relapsed/Refractory B-Cell Malignancies

Abstract 1529

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INTRODUCTION

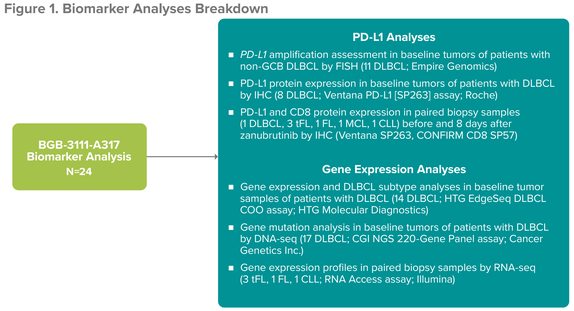
- DLBCL, an aggressive B-cell lymphoma, is the most common type of NHL worldwide[1]
- Approximately one-third of patients are refractory to or relapse after standard therapy[2]
- The antitumor efficacy of zanubrutinib, a selective irreversible next-generation BTK inhibitor, and tislelizumab, a PD-1 receptor monoclonal antibody approved for 8 indications in China, has been demonstrated in patients with B-cell malignancies, including DLBCL[3,4]
- BGB-3111-A317 (NCT02795182) is a phase 1 study (now closed) assessing the safety, tolerability, and antitumor activities of zanubrutinib and tislelizumab combination therapy in B-cell malignancies
- Comprehensive biomarker analyses were performed in patients with B-cell malignancies from the BGB-3111-A317 study to examine biomarkers associated with response or resistance to zanubrutinib and tislelizumab combination therapy

OBJECTIVES

- To explore the biomarkers that change in the TME in responding to zanubrutinib and tislelizumab combination therapy
- To identify the mechanisms of response and resistance to zanubrutinib and tislelizumab combination therapy

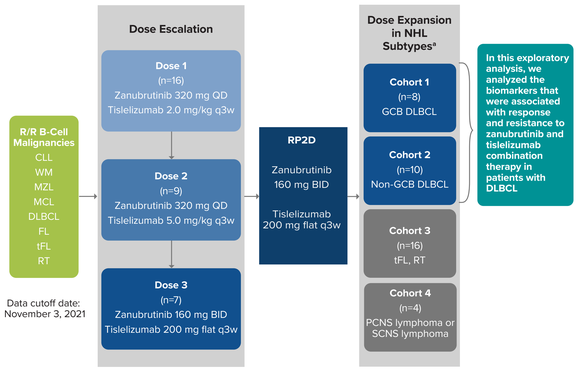
METHODS

Figure 1. Biomarker Analyses Breakdown



- Samples from 24 patients enrolled in the BGB-3111-A317 study were used for biomarker analysis and their response data were accessed and published by the investigator using Lugano 2014 criteria[5]

Figure 2. BGB-3111-A317 Study Design



[a]Cohorts 1, 2, and 4 had slots available for up to 10 patients; cohort 3 had slots available for up to 20 patients.

RESULTS

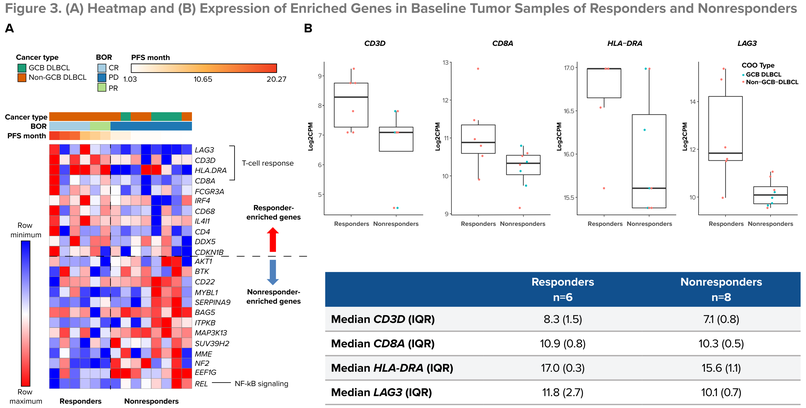
Table 1. The Correlation Between the Expression and Gene Alteration of *PD-L1* and the Clinical Response

	DLBCL					Non-GCB[d]				
	All patients N=27	With available *PD-L1* expression data			Without available data[b] n=19	All patients N=15	With available *PD-L1* FISH data			Without available *PD-L1* FISH data n=4
		With PD-L1 TC expression[a] n=2	Without PD-L1 TC expression n=6	All with available data n=8			With *PD-L1* alteration[c] n=2	Without *PD-L1* alteration n=9	All with available data n=11	
ORR, n (%)	9 (33)	1 (50)	2 (33)	3 (38)	6 (32)	6 (40)	2 (100)	3 (33)	5 (45)	1 (25)
CR, n (%)	6 (22)	1 (50)	1 (17)	2 (25)	4(21)	4 (27)	2 (100)	2 (22)	4 (36)	0

[a]One patient was treated with dose 1. [b]Two patients were treated with dose 1. [c]One patient was treated with dose 1. [d]Only 4 patients with GCB DLBCL had available *PD-L1/2* gene alteration data. No *PD-L1* gene alteration was observed.

- Patients with PD-L1+ tumor cells and *PD-L1* gene alteration were more responsive to zanubrutinib and tislelizumab combination therapy

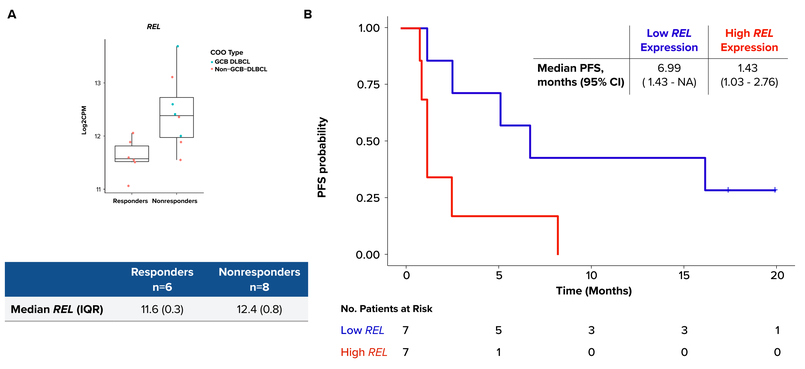
Figure 3. (A) Heatmap and (B) Expression of Enriched Genes in Baseline Tumor Samples of Responders and Nonresponders



	Responders n=6	Nonresponders n=8
Median *CD3D* (IQR)	8.3 (1.5)	7.1 (0.8)
Median *CD8A* (IQR)	10.9 (0.8)	10.3 (0.5)
Median *HLA-DRA* (IQR)	17.0 (0.3)	15.6 (1.1)
Median *LAG3* (IQR)	11.8 (2.7)	10.1 (0.7)

- High mRNA levels of *CD3D*, *HLA-DRA*, and *LAG3* were enriched in baseline tumor samples of responders

Figure 4. (A) Expression of *REL* in Responders and Nonresponders and (B) PFS According to *REL* Expression in Patients With DLBCL

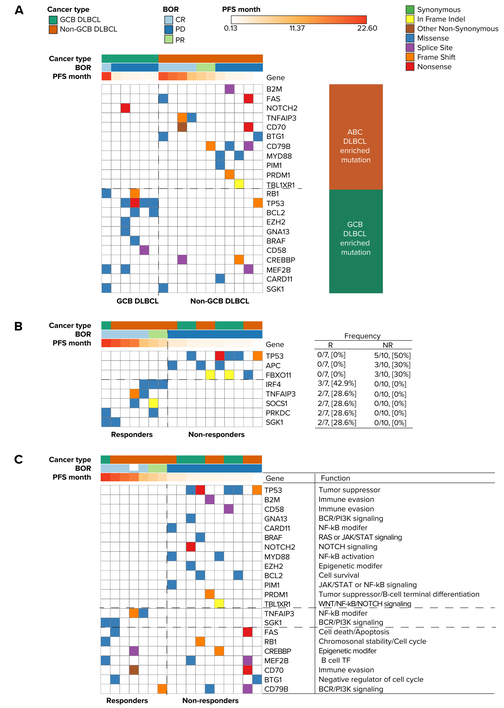


	Low *REL* Expression	High *REL* Expression
Median PFS, months (95% CI)	6.99 (1.43 - NA)	1.43 (1.03 - 2.76)

	Responders n=6	Nonresponders n=8
Median *REL* (IQR)	11.6 (0.3)	12.4 (0.8)

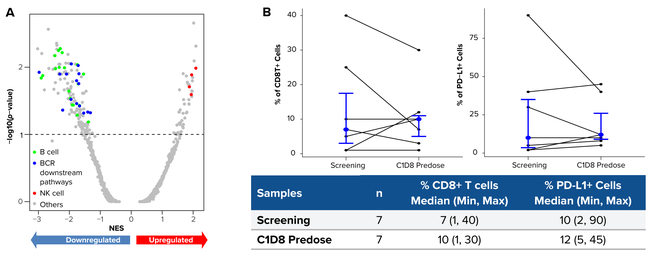
- High mRNA levels of *REL* were found in nonresponders and were associated with poor clinical outcome after zanubrutinib and tislelizumab combination therapy

Figure 5. (A) Distribution of COO-Subtype Enriched Mutations in Patients With GCB and Non-GCB DLBCL and (B) Heatmap of Enriched Gene Mutations and (C) Recurrent DLBCL Gene Mutations in Responders and Nonresponders



- Mutations in *TP53* were enriched in nonresponders

Figure 6. (A) Gene Signature Enrichment Analysis Between Baseline and Post-Zanubrutinib Treatment and (B) *PD-L1* and *CD8* Expression in Paired Tumor Samples by IHC



Samples	n	% CD8+ T cells Median (Min, Max)	% PD-L1+ Cells Median (Min, Max)
Screening	7	7 (1, 40)	10 (2, 90)
C1D8 Predose	7	10 (1, 30)	12 (5, 45)

- Inhibition of B-cell and BCR-related signatures and induction of NK signatures were observed in tumor samples on zanubrutinib treatment
- The frequency of PD-L1+ cells or CD8+ cells in the TME were not changed upon zanubrutinib treatment

CONCLUSIONS

- Preliminary data suggest that patients with *PD-L1* gene amplification, PD-L1+ tumor cells, and high mRNA levels of *CD3D*, *HLA-DRA*, and *LAG3* in baseline tumor tissue may be more responsive to zanubrutinib and tislelizumab combination therapy
- High mRNA levels of *CD3D*, *HLA-DRA*, and *LAG3* were enriched in baseline tumor samples of responders, which may suggest an inflamed TME
- High mRNA levels of *REL* were observed in nonresponders and were associated with poor clinical outcomes to zanubrutinib and tislelizumab combination therapy
- A higher frequency of mutations in *TP53* was found in nonresponders and may contribute to resistance to zanubrutinib and tislelizumab combination therapy
- Inhibition of B-cell and BCR-related signatures and induction of NK signatures in tumor samples on zanubrutinib treatment indicate the on-target effect of zanubrutinib treatment and its potential effect on TME modulation
- Due to the limited number of samples, results must be interpreted with caution and generalization beyond this study is not conclusive

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ABBREVIATIONS

ABC, activated B-cell; BCR, B-cell receptor; BID, twice daily; BOR, best overall response; BTK, Bruton tyrosine kinase; CD3D, CD3 delta subunit of T-cell receptor complex; CD84, cluster of differentiation 84; CLL, chronic lymphocytic leukemia; COO, cell of origin; CPM, count per million reads; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; GCB, germinal center B-cell like; *HLA-DRA*, major histocompatibility complex, Class II, DR alpha; IgG, immunoglobulin; IHC, immunohistochemistry; IQR, interquartile range; JAK, janus kinase; LAG3, lymphocyte activating 3; max, maximum; MCL, mantle cell lymphoma; min, minimum; MZL, marginal zone lymphoma; NA, not available; NES, normalized enrichment score by GSEA analysis; NF-KB, nuclear factor kappa B; NHL, non-Hodgkin lymphoma; NK, natural killer; NOTCH, neurogenic locus notch homolog protein; NR, not reached; ORR, overall response rate; PCNS, primary central nervous system; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, partial response; q3w, every 3 weeks; QD, once daily; R/R, relapsed or refractory; REL, REL proto-oncogene; RP2D, recommended phase 2 dose; RT, Richter transformation; SCNS, secondary central nervous system; STAT, signal transducer and activator of transcription; TC, tumor cell; tFL, transformed follicular lymphoma; TME, tumor microenvironment; WM, Waldenström macroglobulinemia.

DISCLOSURES

JL, XM, RH: Employment and stock with BeiGene.
LZ: Employment and stock with RiboX Therapeutics, Ltd.; former employment with BeiGene.
YY: Employment with BMS; former employment with BeiGene.
OP: Employment and stock with BeiGene; former employment with Eli Lilly.
YL: Employment and stock with BeiGene (Shanghai) Co., Ltd.
JH: Employment, stock, and divested equity ownership with BeiGene.

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