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

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INTRODUCTION

- DLBCL, an aggressive B-cell lymphoma, is the most common type of NHL worldwide.
- Approximately one-third of patients are refractory to or relapse after standard therapy.
- The prevalent BCR pathway as well as its downstream families, B-cell receptor and downstream, a PD-1 receptor monoclonal antibody approved for use in China, has been demonstrated to patients with B-cell malignancies, including DLBCL.
- BGB-281-037 (BCT007/5G6) is a phase 1 study (now closed) assessing the safety, tolerability, and antitumor schedules of zanubrutinib and tislelizumab combination therapy in B-cell malignancies.
- Comprehensive biomarker analyses were performed in patients with B-cell malignancies from the BGB-281-037 study to identify 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

- Samples from 24 patients enrolled in the BGB-281-037 study were used for biomarker analysis and their response data were analyzed and published by the investigator using Illumina 2014 criteria.
- Expression in Patients With DLBCL

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

RESULTS

- Gene expression profiles in paired biopsy samples by RNA-seq.
- PD-L1 and CD8 protein expression in paired biopsy samples by DNA-seq.
- (1 DLBCL, 3 tFL, 1 FL, 1 MCL, 1 CLL) before and 8 days after treatment with zanubrutinib and tislelizumab.

CONCLUSIONS

- Preliminary data suggest that patients with PD-L1+ gene amplification, PD-L1+ tumor cells, and high mRNA levels of CD30, HLA-DRA, and LAG3 are less likely to have baseline tumor samples of responders.
- High mRNA levels of CD30, HLA-DRA, and LAG3 were identified in baseline tumor samples of responders, which may suggest an impaired TME.
- High mRNA levels of IBE were observed in nonresponders and were associated with poor clinical outcomes in zanubrutinib and tislelizumab combination therapy.
- A higher frequency of mutations in TP53 was found in nonresponders and may contribute to the response 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 indicated the off-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 concluded.