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

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Background

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

Aims

This study evaluated potential biomarkers that can predict zanubrutinib response in R/R non-GCB DLBCL.

Methods

A total of 121 patients with R/R non-GCB DLBCL defined by immunohistochemistry (Hans algorithm) were recruited in four zanubrutinib studies that were conducted at a similar time period. Two of the four studies were zanubrutinib monotherapy (n = 79) and two were zanubrutinib combined with an anti-CD20 antibody therapy (n = 42). Similar inclusion and exclusion criteria and response evaluation criteria were used across all studies. Fifty-six non-GCB patients were further subtyped by gene expression profiling (GEP) using the HTG EdgeSeq DLBCL Cell of Origin Assay. The expression of approximately 90 lymphoma-associated genes from the HTG GEP assay were analyzed using R package limma for correlation with response to zanubrutinib treatment. The gene mutations of seventy-seven patient samples were tested by next-generation sequencing (NGS) with a panel of genes. Chi-square test was used to evaluate the association between mutations and the objective response rate (ORR). Study effect was adjusted as well.

Results

The unadjusted ORR in non-GCB DLBCL was between 23% and 35% for the four studies. For 49 patients with GEP-confirmed activated B-cell (ABC) DLBCL classification, the ORR was between 36% and 54% and comparable for monotherapy (42.1%) and combination therapy (45.5%). For the 56 non-GCB patients with HTG gene expression profiles, *PAX5* expression was significantly higher in monotherapy responders, and *PIM1*, *BCL2*, and *FOXP1* expression was higher in combination therapy responders. Patients with MYC and BCL2 double expressor DLBCL tended to have higher ORRs (11/18, 61% vs 11/38, 29%; $P = 0.12$) and longer progression-free survival (5.4 months vs 3.6 months; $P = 0.16$) and overall survival (10 months vs 7 months, $P = 0.32$), although not reaching nominal statistical significance. For the 77 patients with NGS panel data, mutations in B-cell receptor pathway or NOTCH1 pathway genes were correlated with better response. Patients with non-GCB DLBCL with *CD79B* mutations (n = 25) showed significantly higher ORR than

Conclusion

Zanubrutinib alone or in combination with an anti-CD20 antibody 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.