INTRODUCTION

- The non-geminal center B-cell-like (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL) is associated with poor clinical outcomes.
- Zanubrutinib, a selective covalent Bruton’s tyrosine kinase (BTK) inhibitor, was specifically engineered to decrease toxicities and improve tumor tissue distribution.
- Inhibitors of 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.

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 2.8 to 4.9m, and median OS ranged from 8.4m to 11.8m. (Table 1)

<table>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>Study 1 (n=38)</th>
<th>Study 2 (n=41)</th>
<th>Study 3 (n=22)</th>
<th>Study 4 (n=20)</th>
<th>Total (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>37.8 (14/38)</td>
<td>31.7 (13/41)</td>
<td>32.7 (7/22)</td>
<td>25.0 (5/20)</td>
<td>30.5 (42/138)</td>
</tr>
</tbody>
</table>

- 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>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>Study 1 (n=14)</th>
<th>Study 2 (n=13)</th>
<th>Study 3 (n=7)</th>
<th>Study 4 (n=6)</th>
<th>Total (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>57.1 (8/14)</td>
<td>23.1 (3/13)</td>
<td>28.6 (2/7)</td>
<td>33.3 (2/6)</td>
<td>35.7 (15/42)</td>
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</tbody>
</table>

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

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

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

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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REFERENCES


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