Development of a Bruton’s Tyrosine Kinase (Btk) inhibitor - ONO-WG-307, a potential treatment for B-cell malignancies

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ABSTRACT

Purpose: Signals from B cell receptors (BCR) play a central role in signal transduction pathways regulating survival, activation, proliferation, and differentiation of B-lineage lymphoid cells. BCR signaling is implicated in the pathogenesis of B-cell lymphoproliferative diseases. Anti-BCR therapy (rituximab) is considered standard of care for B-cell lymphomas, but new treatments are needed. Btk is a key enzyme in the BCR signaling pathway, and its inhibition could constitute a promising new strategy for the treatment of B-cell malignancies.

INTRODUCTION

• Signals from B-cell receptors (BCR) play a central role in signal transduction pathways, by regulating survival, activation, proliferation, and differentiation of B-lineage lymphoid cells. BCR signaling is implicated in the pathogenesis of B-cell lymphoproliferative diseases.

• Rituximab (RTX) inhibits BCR signaling by targeting proximal components of the BCR cascade. RTX has significant impact on the cells, which are subject to BCR stimulation.

• DLBCL is the most common malignant lymphoma with studies indicating that chronic, active BCR signaling is frequently observed in this disease.

• Btk is a key enzyme in the BCR signaling pathway, and its inhibition could constitute a promising new strategy for the treatment of B-cell malignancies.

MATERIAL AND METHODS

ONO-WG-307 was tested in a Btk inhibitor panel to measure selectivity and activity in different Btk-expressing cell lines. The IC50 values were determined for Btk, Fyn, Lyn, and Lck in the assay. In vitro cytotoxic activity of ONO-WG-307 was determined using a cell viability assay.

RESULTS

ONO-WG-307 is a highly potent and selective Btk inhibitor with an IC50 in the sub-nmol/L range. ONO-WG-307 is a promising new candidate targeted agent for ABC-BCLB and support the potential clinical utility of ONO-WG-307 in the treatment of B-cell malignancies.

CONCLUSIONS

ONO-WG-307 is a highly potent and selective Btk inhibitor with preliminary evidence of efficacy in an ABC-DLBCL xenograft model along with an anti-proliferative effect in a range of NHL and CLL cell lines.

SIGNIFICANCE

ONO-WG-307 is a highly potent and selective Btk inhibitor with evidence of efficacy in the treatment of B-cell malignancies.

Figure 3. Continuous exposure of ONO-WG-307 is required to kill TMD-8 cells

Figure 4. Anti-tumor activity of ONO-WG-307 in TMD-8 xenograft model

Figure 5. Effect of anti-IgM2 on BCR activation in TMD-4 and DOHH2 cell lines

SIGNIFICANCE

ONO-WG-307 is a highly potent and selective Btk inhibitor with evidence of efficacy in the treatment of B-cell malignancies.

Table 1. ONO-WG-307 inhibits proliferation in a range of NHL/CLL cell lines

Table 2. Rituximab inhibits proliferation of TMD-4 and DOHH2 cell lines

CONCLUSIONS

ONO-WG-307 is a promising new candidate targeted agent that is being developed for the treatment of B-cell lymphoproliferative diseases and our results support the potential clinical utility of ONO-WG-307 in the treatment of B-cell malignancies.