BGB-16673: A BTK Degrader, Overcomes On-Target Resistance From BTK Inhibitors And Presents Sustainable Long-Term Tumor Regression In Lymphoma Xenograft Models

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INTRODUCTION

• Bruton tyrosine kinase (BTK) is a key component of the BCR signaling pathway whose chronic activation is critical for cell proliferation and survival in various B cell malignancies. Inhibition of BTK by covalent BTK inhibitors (cBTKis), such as ibrutinib, acalabrutinib, and zanubrutinib, have revolutionized the management of CLL and other B cell malignancies. However, frequently acquired BTK resistant mutations at cysteine 481, which abrogate cBTK binding capacity, and other mutations inducing kinase hyperactivation or kinase independent function, limit long-term clinical benefit.

• Non-covalent BTK inhibitors (e.g., pirtobrutinib) have demonstrated promising efficacy in CLL patients with BTK C481 mutations who progressed on cBTKis. Even so, BTK mutations beyond BTK C481 are emerging in patients. Agents which could tackle resistance mutations from both covalent and non-covalent BTKis may provide novel treatment options. Moreover, though BTK dependency for certain aggressive lymphomas is well documented, the clinical benefit of approved BTKis seems to be modest and further clinical investigation is warranted. A compound with BTK degradation may bring additional advantage over BTK inhibition for those aggressive diseases.

• BGB-16673 is an orally available BTK-targeting chimeric degradation activation (BTK-CDAC) compound designed to degrade wildtype BTK and multiple mutant forms. It is currently under investigation in two phase I studies (NCT05006716, NCT05294731).

• BGB-16673 is a potent degrader against tumors expressing wildtype and clinical-relevant BTK mutations resistant to both covalent and non-covalent BTK inhibitors from panels A-F. BTK C481 substitutions have the potential to confer resistance to covalent and non-covalent BTKis in cell lines and mouse xenograft models. Additionally, BTK and downstream phosphorylation events in relevant cell lines were evaluated. We further examined whether BGB-16673 is superior to BTKis in suppressing tumor growth and metastasis.

OBJECTIVE

Here, we investigated the capability of BGB-16673 to overcome commonly observed -target mutations from both covalent and non-covalent BTK inhibitors in cell lines and mouse xenograft models. Additionally, BTK and downstream phosphorylation events in relevant cell lines were evaluated. We further examined whether BGB-16673 is superior to BTKis in suppressing tumor growth and metastasis.

METHODS

• TMD-8 cells expressing wildtype or mutant BTK were incubated with BTK inhibitors and BGB-16673. Cell viability was measured by CTG assay. Cell viability was measured by CTG assay.

• Western blot was utilized to detect phosphorylation of BTK (Y223 and PLCγ2 Y1217).

• Wildtype or mutant BTK-expressing TMD-8 cells were inoculated subcutaneously into NCG mice for in vivo efficacy determination.

• Comparisons between groups were performed using unpaired t tests.

RESULTS

Figure 1. BGB-16673 exhibits high potency on clinically relevant BTK mutants resistant to covalent and non-covalent BTK inhibitors in cancer cells in vitro

• BGB-16673 exhibits high potency on clinically relevant BTK mutants resistant to covalent and non-covalent BTK inhibitors in cancer cells in vitro. Table 1. Demographic and Baseline Disease Characterization

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CONCLUSION

• BGB-16673 is a potent degrader against tumors expressing wildtype and clinical-relevant BTK mutations. In addition, BGB-16673 exhibits longer duration of response and less metastatic infiltration to the spleen than brutinib and pirtobrutinib.

REFERENCES


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