

Abstract: P1219

Title: BGB-16673, A BTK DEGRADER, OVERCOMES ON-TARGET RESISTANCE FROM BTK INHIBITORS AND PRESENTS SUSTAINABLE LONG-TERM TUMOR REGRESSION IN LYMPHOMA XENOGRRAFT MODELS

Abstract Type: Poster Presentation

Session Title: Lymphoma Biology & Translational Research

Background:

Bruton tyrosine kinase (BTK) is a key kinase in chronic BCR signaling which is critical for cell proliferation and survival in various B cell malignancies. Inhibition of BTK by covalent BTK inhibitors (BTKi), such as ibrutinib, acalabrutinib, and zanubrutinib, have revolutionized the management of CLL and other B cell malignancies. However, frequently acquired BTK resistant mutations at cystine 481, which abrogate BTKi binding capacity, and other mutations inducing kinase hyperactivation or kinase independent function, limits long-term clinical benefit. Thus, therapies capable of preventing or overcoming covalent BTKi resistance are needed. Non-covalent BTK inhibitors (eg, LOXO-305), designed to overcome BTK C481 mutations, demonstrated promising efficacy in CLL patients with C481X mutations progressed from prior covalent BTK inhibitors. However, new BTK mutations beyond BTK C481X emerged during disease progression. Agents which could tackle resistance from both covalent and non-covalent BTKis-induced mutations may provide novel treatment options. While the dependency on BTK for certain aggressive lymphomas is well documented, the clinical benefit of approved BTKis seems to be modest and further clinical investigation is warranted. Instead of kinase inhibitors, a compound with BTK-targeted degradation may bring additional advantage over BTK kinase activity inhibition for those aggressive diseases.

BGB-16673 is an orally available BTK-targeting chimeric degradation activation compound designed to degrade wildtype BTK and multiple mutant forms. It is currently under phase 1 clinical investigations (NCT05006716, NCT05294731).

Aims:

Here, we investigate the capability of BGB-16673 against frequent on-target mutations from covalent and non-covalent BTKis in cell lines and mouse xenograft models. Additionally, BTK and downstream phosphorylation events in relevant cell lines are evaluated. We further examined whether BGB-16673 is superior to BTKIs in suppressing tumor growth and metastasis.

Methods:

The viability of TMD-8 cells expressing wild type or mutant BTK were measured by CTG assay. Western blot was utilized to detect specific signaling proteins. TMD-8 cells expressing wild type or mutant BTK were inoculated subcutaneously into NCG mice and used for *in vivo* efficacy determination. Unpaired t test was performed for statistical analysis.

Results:

BGB-16673 presents potent anti-proliferation activity in TMD-8 lymphoma cells expressing wildtype BTK or C481S, T474I, L528W mutants, and is superior to ibrutinib and LOXO-305. Consistently, BGB-16673 exhibits deeper inhibition of BTK and PLC γ 2 phosphorylation in C481S, T474I and L528W mutants than ibrutinib and LOXO-305. In xenograft models, BGB-16673 drives complete regression of tumors harboring BTK C481S, T474I, L528W mutations, implying its ability to overcome major on-target resistance induced by both covalent and non-covalent BTKis. In addition, BGB-16673 more efficiently controls large tumors at initiation of treatment to mimic bulky/aggressive situations in clinic. Notably, when compared with ibrutinib and a clinical investigational inhibitor, (LOXO-305, BGB-16673 shows significantly longer duration of complete response and less spleen metastasis, suggesting its potential advantages over other BTK inhibitors in long-term clinical benefit.

Summary/Conclusion:

BGB-16673 is a potent inhibitor against tumors expressing wildtype and clinical-relevant BTK mutations. In addition, it is superior to ibrutinib and LOXO-305 equivalent for more durable anti-tumor activities and less metastasis.

Keywords: Absolute lymphocyte count, Tumor model, Lymphoma, Mouse model