BGB-16673, a selective BTK degrader, exhibits deeper inhibition of cancer cell signaling pathways and better efficacy in MCL models

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Introduction:

Cell cycle dysregulation, B cell receptor (BCR) signaling, and constitutive NFκB activation are key aberrations in the pathogenesis of mantle cell lymphoma (MCL) (Jain and Wang, 2022). BCR signaling is crucial for the proliferation, survival, and migration of lymphoma cells, with BTK, a non-receptor protein kinase, playing a pivotal role (Young and Staudt, 2013). Over the past decade, the development and approval of covalent BTK inhibitors (cBTKis) like ibrutinib, acalabrutinib, and zanubrutinib, as well as the non-covalent BTK inhibitor (ncBTKi) pirtobrutinib, have marked substantial progress of targeting BTK in MCL. However, effective treatments are still needed for patients with acquired or refractory resistance to these BTK inhibitors.

Resistance mechanisms to BTKis in MCL is not fully understood. Unlike CLL/SLL, BTK mutations are less common in MCL. Whether BTK inhibitor resistant MCL cells still rely on BTK signaling remains to be determined. The 57.8% overall response rate of pirtobrutinib in MCL patients with prior cBTKi treatments suggests that most BTKi-pretreated patients still have BTK dependency (Wang et al., 2023), indicating the potential benefit of a different BTK inhibition strategy.

BGB-16673 is an orally available BTK-targeting chimeric degradation activation compound (CDAC). It is currently under investigation in two phase I studies (NCT05006716, NCT05294731), and has shown promising efficacy in patients with B-cell malignancies, including MCL (Seymour et al., 2023). Unlike BTK inhibitors which inhibit the kinase activity of BTK, BGB-16673 degrades the entire BTK protein. This comprehensive inhibition may address potential scaffold functions of BTK, as suggested by kinase-dead BTK mutations in BTKi-progressed patients (Montoya et al., 2024). Previous studies have shown that BGB-16673 can counteract BTK mutations from both c- and nc-BTK inhibitors, such as BTK-C481S, T474I, and L528W (Wang et al., 2023). Here, we investigated whether BGB-16673 has better efficacy in a BTKi partial-sensitive wildtype BTK expressing MCL model REC-1 and explored the underlying mechanisms through RNA-seq analysis of drug-treated tumors.

Results:

To evaluate the efficacy of BGB-16673, REC-1 cancer cells were implanted subcutaneously into NCG mice and treated with BGB-16673 at its clinically achievable dose 6 and 20 mg/kg. BGB-16673 effectively inhibited tumor growth at both doses, showing dose dependency. When compared with BTKis that have received accelerated approval for R/R MCL at their clinically relevant dose, BGB-16673 at both doses showed better efficacy.

To explore the underlying mechanisms of better efficacy, RNA-seq was performed on drug-treated tumors (n=4 per treatment). Principal component analysis (PCA) of the RNA-seq data revealed three distinct clusters, separating BGB-16673 from BTKis and vehicle groups, indicating a unique biological effect of BGB-16673. GO term enrichment analysis of the RNA-seq data showed that both BGB-16673 and BTKis inhibited gene expression related to cell cycle and BCR signaling pathways. However, BGB-16673 resulted in greater inhibition of cell-cycle-related genes, correlating with its superior efficacy in inhibiting cancer cell growth. Additionally, BGB-16673 more effectively inhibited NFκB targets and certain Bcl-2 family members. Given that multiple Bcl-2 inhibitors are also in development in MCL, and Bcl-2 family members contribute to the resistance of Bcl-2 inhibitor, this finding supports the rationale for combining BTK and Bcl-2 targeting compounds in MCL.

Conclusions:

BGB-16673 has better efficacy than BTK inhibitors in MCL model REC-1. The enhanced efficacy correlated with its deeper inhibition of cancer cell signaling pathways in tumor. Results also support the combination of BGB-16673 with Bcl-2 inhibitors in MCL. These discoveries highlight the potential of BGB-16673 in treating MCL patients.