Title: Sonrotoclax (BGB-11417), a selective Bcl-2 inhibitor, demonstrates better efficacy than Venetoclax (Ven) and Lisaftoclax (APG-2575) in hematological cancer cells, xenografts, and human bloods

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Background:

Bcl-2 overexpression, a hallmark of hematologic malignancies, is associated with cell death evasion and drug resistance. Bcl-2 inhibitors such as Ven counteract this by disrupting Bcl-2 interaction with pro-apoptotic proteins (e.g., BIM), thereby restoring apoptosis.

Despite Ven's clinical success, limitations like tumor lysis syndrome and suboptimal complete remission (CR) rates in CLL (chronic lymphocytic leukemia), underscore the need for improved inhibitors. Lisaftoclax (Lisa) and sonrotoclax (Son), are other two Bcl-2 inhibitors at late-stage of development. However, how are the three Bcl-2 inhibitors different from each other is unknown. This study investigates the difference of Ven, Lisa, and Son in different model systems.

Methods

RS4;11- and KMS-12-PE- Bcl-2-G101V cells were generated by ENU mutagenesis. OCI-LY10 expressing BTK-WT and mutations were engineered using lentiviral transduction. *In vitro* cytotoxicity was assessed via CellTiter-Glo (CTG) assay. Bcl-2:BIM complex disruption were examined by MSD assay.

Results

In vitro cytotoxicity assay revealed higher potency of Son compared to Ven and Lisa in Bcl-2-dependent cell lines across different indications. In Bcl-2-G101V mutant cells—a mutation presented in ~30% of Ven-relapsed CLL patients—Son retained >10-fold higher potency than Ven and Lisa. Moreover, Son also presented better efficacy than Ven and Lisa in different xenografts in vivo.

Given Bcl-2 inhibitors are often used with/after BTK inhibitors in treating B cell lymphoma like CLL, MCL (mantle cell lymphoma), where BTK mutations contributing to resistance, Bcl-2 inhibitors were also profiled on B lymphoma cancer cells expressing BTK mutations. Intriguingly, Son maintained similar activity in OCI-LY10 cells expressing wildtype BTK as in BTK mutations (C481S, T474I, L528W, A428D), where Ven and Lisa exhibited less potent activity.

Mechanistically, Son induced stronger Bcl-2:BIM disruption and caspase-3 activation in cancer cells, correlating with enhanced apoptosis. In human, Bcl-2 inhibitor effect is confounded by plasma protein binding (PPB). To understand potential difference in human under PPB, human whole blood from healthy donors was treated with Son, Ven, Lisa, the Bcl-2:BIM protein complex disruption—the very proximal and direct effect of Bcl-2 inhibitors—was then examined. Human whole blood assays also demonstrated that Son has >10-fold lower IC90

than Ven and Lisa in disrupting Bcl-2:BIM.

Conclusions

Son demonstrates significant advantage over Ven and Lisa in preclinical studies, including better efficacy in Bcl-2-dependent cancers, against Bcl-2-G101V and BTK resistance mutations, and enhanced target engagement in human whole blood. These highlight Son's great potential in addressing unmet needs in hematologic malignancies.