BGB-21447, a Next-generation BCL-2 Inhibitor, Demonstrates Superior Potency to Venetoclax and Overcomes Diverse BCL-2 Mutations in Preclinical Models of Hematologic Malignancies

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Bcl-2 is a key anti-apoptotic gatekeeper that controls intrinsic apoptosis pathway. Its overexpression or aberrant activation is frequently observed in hematologic malignancies, where it promotes tumorigenesis and confers resistance to chemotherapy. Venetoclax (VEN), the first-in-class Bcl-2 inhibitor approved for R/R CLL and AML, shows modest efficacy in non-Hodgkin lymphoma and is compromised by acquired BCL2 mutations (e.g., G101V, D103Y).

Herein, we report the preclinical characterization of BGB-21447, a highly potent and selective next-generation Bcl-2 inhibitor that demonstrates remarkably better potency over VEN across multiple hematologic cancer cell lines and effectively targets a broad spectrum of VEN-resistant Bcl-2 mutations.

BGB-21447 displays ≥121-fold higher selectivity for Bcl-2 over Bcl-xL, Bcl-W, Mcl-1 and Bcl2A1. Across a panel of 9 hematologic lines, it consistently achieved lower IC_{50} values than VEN (0.18-6.6 nM vs 4.8-238 nM for Ven). In RS4;11 cells overexpressing Bcl2 mutants, BGB-21447 achieved IC_{50} values of 11-44 nM IC_{50}s, including G101V (15 nM vs 3854 nM for VEN) and D103Y (44 nM vs 4731 nM). Its anti-proliferative effects were accompanied by hallmark features of intrinsic apoptosis, including caspase-3/7 activation, phosphatidylserine externalization (Annexin V positivity), and sub-G0/G1 DNA accumulation.

In PK/PD studies, oral administration of BGB-21447 demonstrated a clear exposure-response relationship in both RS4;11 wild-type and Bcl-2-G101V knock-in xenograft models, with cleaved caspase-3 levels correlating with intratumoral drug concentration. At 1 mg/kg, BGB-21447 showed superior antitumor efficacy compared to VEN at 15 mg/kg in the RS4;11 WT model. Notably, BGB-21447 showed robust antitumor effects in VEN-insensitive models, including the Toledo (DLBCL), RS4;11 Bcl2-G101V, and RS4;11 Bcl2-D103Y xenografts. No significant weight loss or laboratory toxicities were observed.

In conclusion, BGB-21447 surpasses VEN in potency and mutant coverage, and durably inhibited VEN-resistant tumors at well-tolerated doses. These findings support the ongoing Phase 1 clinical trials (NCT05828589, NCT06756932) evaluating BGB-21447 in B-cell malignancies and metastatic breast cancer.