A PHASE 1 FIRST-IN-HUMAN STUDY OF BGB-16673, A BRUTON TYROSINE KINASE PROTEIN DEGRADER, IN PATIENTS (PTS) WITH B-CELL MALIGNANCIES (TRIAL IN PROGRESS)

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Background: Bruton tyrosine kinase (BTK) functions downstream of the B-cell antigen receptor (BCR) and plays a critical role within the BCR signaling pathway and the pathogenesis of several B-cell malignancies. BTK inhibitors (BTKi) have revolutionized management of B-cell malignancies. However, resistance caused by BTK mutations, which can abrogate BTKi binding capacity or BTK scaffold function, or cause kinase hyper activation, may limit therapeutic options in subsequent lines of therapy. Re-challenging patients with agents that can overcome the resistance due to BTK mutations may provide a novel treatment option. BGB-16673 is an investigational, orally available agent with preclinically demonstrated BTK degradation activity against both wild type and mutant forms commonly identified in pts who have progressed on BTKi.

Aims: In the dose-escalation part of the study, we aim to assess the safety and tolerability of BGB-16673 in selected relapsed or refractory (R/R) B-cell malignancies, to characterize its pharmacokinetic (PK) and pharmacodynamic (PD) profiles, to determine a recommended phase 2 dose (RP2D) and to evaluate anti-tumor activity. In the dose-expansion part of the study, we aim to evaluate the safety, tolerability, PK, PD, and anti-tumor activity under the RP2D in pts with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL).

Methods: BGB-16673-101 (NCT05006716) is a phase 1 open-label, dose-escalation and -expansion study evaluating BGB-16673 in adult pts with R/R B-cell malignancies. Key inclusion criteria include confirmed diagnosis of R/R B-cell malignancy (including marginal zone lymphoma, follicular lymphoma, MCL, CLL/SLL, and Waldenström macroglobulinemia [WM]), Eastern Cooperative Oncology Group performance status score of 0 to 2, and adequate organ function. Key exclusion criteria include current or history of central nervous system involvement, autologous stem cell transplant (ASCT) within 3 months or chimeric antigen receptor T cell therapy or allogeneic SCT within 6 months of the first dose of BGB-16673 or requiring treatment with strong inhibitors or inducers of CYP3A. All pts will be followed for safety and tolerability, including treatment-emergerent adverse events that occur during treatment and up to 30 days after treatment discontinuation, or until the initiation of another anti-cancer therapy, whichever occurs first. The totality of the available safety, efficacy, PK, and PD data from the dose-escalation part will be used by the Safety Monitoring Committee to determine the RP2D. The dose-expansion part will commence subsequent to RP2D determination. Responses will be evaluated per the 2014 Lugano Classification, the 2018 International Workshop on CLL guidelines response assessment with modification for treatment-related lymphocytosis, or the 6th International Workshop on WM.
consensus criteria. Additional efficacy analyses will include progression-free survival and overall survival. All pts will give informed consent.

**Results:** This is a trial in progress; safety and tolerability results of BGB-16673 are expected.

**Conclusion/Summary:** BGB-16673-101 is the first in-human study of the BTK degrader BGB-16673.