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-emergent 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.