CaDAnCe-304, a phase 3, open-label, randomized study to evaluate the safety and efficacy of Bruton tyrosine kinase degrader BGB-16673 compared with pirtobrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma

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Introduction: Targeting Bruton tyrosine kinase (BTK) has revolutionized the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Pirtobrutinib, a noncovalent BTK inhibitor, was recently approved for patients who relapsed following covalent BTK inhibitor therapy such as ibrutinib, acalabrutinib, or zanubrutinib. BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. Data from CaDAnCe-101 (BGB-16673-101, NCT05006716), an ongoing phase 1/2 study, demonstrates that BGB-16673 has a tolerable safety profile and can achieve responses in heavily pretreated patients with relapsed/refractory (R/R) CLL/SLL, including those with prior BTK inhibitor treatment and *BTK* resistance mutations. Here, a phase 3 study that will evaluate the efficacy and safety of BGB-16673 vs pirtobrutinib in patients with R/R CLL/SLL previously treated with a covalent BTK inhibitor is described.

Methods: CaDAnCe-304 (BGB-16673-304, NCT06973187) is an open-label, randomized, phase 3 clinical study. Eligible patients are aged ≥18 years and have a confirmed diagnosis of CLL/SLL that is R/R after ≥1 line of therapy, including a covalent BTK inhibitor. Patients are excluded if they have prolymphocytic leukemia or a history of Richter transformation, prior exposure to any BTK protein degraders or noncovalent BTK inhibitors, or a history of bleeding disorders. Approximately 500 patients will be enrolled and randomized 1:1 to receive either BGB-16673 (arm A) or pirtobrutinib (arm B). Randomization will be stratified based on prior exposure to BCL2 inhibitors, del(17p) and/or *TP53* mutation status, and response to last covalent BTK inhibitor treatment. The primary endpoint is PFS as determined by an independent review committee (IRC) per modified 2018 International Workshop on CLL criteria (for CLL) and Lugano classification (for SLL). Secondary endpoints include overall survival, PFS by investigator (INV), overall response rate by IRC and INV, rate of partial response with lymphocytosis or higher by IRC and INV, duration of response by IRC and INV, time to next treatment, safety/tolerability per NCI CTCAE v5.0, and patient-reported outcomes. This study is actively recruiting.