CaDAnCe-104, an ongoing, open-label, phase 1b/2 master protocol study of Bruton tyrosine kinase degrader BGB-16673 in combination with other agents in patients with relapsed/refractory B-cell malignancies

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Introduction: Bruton tyrosine kinase (BTK) inhibitors are effective in B-cell malignancies. Despite this, most patients experience disease progression and novel agents active in this setting are needed. 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. In the ongoing CaDAnCe-101 study (BGB-16673-101, NCT05006716), BGB-16673 monotherapy has been generally well tolerated and demonstrated antitumor activity in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), follicular lymphoma (FL), and marginal zone lymphoma (MZL). Based on these results, studies investigating BGB-16673 as part of combination treatments have been designed. Here, an ongoing phase 1b/2 master protocol study that will evaluate the safety and efficacy of BGB-16673 in combination with other agents in patients with R/R B-cell malignancies is described.

Methods: CaDAnCe-104 (BGB-16673-104, NCT06634589) is an open-label, multicenter, phase 1b/2, master protocol study conducted across approximately 49 sites in 8 countries. Patients with the following R/R B-cell malignancies will be included: CLL/SLL, FL, MZL, mantle cell lymphoma (MCL), non-germinal center B-cell like diffuse large B-cell lymphoma (non-GCB DLBCL), Richter transformation, and WM. The current master protocol includes four substudies with their prioritized histologies evaluating BGB-16673 in combination with: sonrotoclax (substudy 1: CLL/SLL, WM, MCL, and MZL), zanubrutinib (substudy 2: CLL/SLL, WM, MCL, and MZL), mosunetuzumab (substudy 3: FL and CLL/SLL), and glofitamab (substudy 4: non-GCB DLBCL and MCL). Each substudy will include a part 1a dose escalation and part 1b safety expansion. Eligible patients are ≥18 years of age with a confirmed diagnosis of an R/R B-cell malignancy with measurable disease. Patients must have adequate organ function (liver, kidney, and bone marrow), adequate washout of prior therapies, and an Eastern Cooperative Oncology Group performance status of 0-2. Patients with non-

GCB DLBCL must have been treated with ≥2 prior lines of therapy, including anthracycline-based and anti-CD20 monoclonal antibody–based regimens. Patients with FL must have received ≥2 prior lines of therapy, including an alkylating agent and an anti-CD20 antibody. The primary endpoints are safety/tolerability per NCI-CTCAE v5.0 and identifying the recommended dose for expansion. Secondary endpoints include overall response rate (assessed according to disease-specific response evaluation criteria), duration of response, time to response, and pharmacokinetic parameters of BGB-16673 and the combination drug in the respective substudies. In addition, several exploratory analyses to assess predictive, prognostic, and pharmacodynamic biomarkers may be performed using patient samples. Recruitment is ongoing.