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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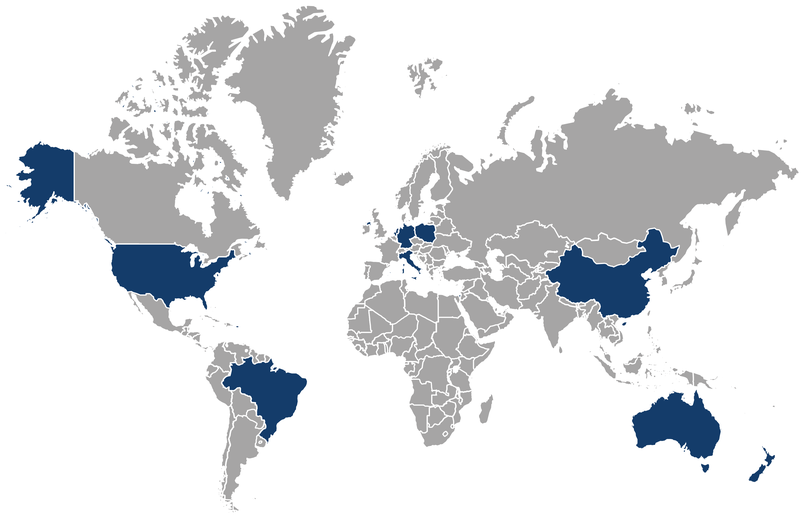
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are effective treatment strategies for patients with certain B-cell malignancies, but most patients eventually experience disease progression, underscoring the need for novel therapeutic approaches including agents that can be used in combination with BTK inhibitors[1-4]
- 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[5]
- By degrading BTK, BGB-16673 disrupts both inherent BTK catalytic activity and its separate protein scaffolding functions, in contrast to small molecule BTK inhibitors that temporarily block BTK catalytic activity alone[6,7]
- The elimination of BTK by degradation may be effective against treatment-resistant BTK mutants that have been shown to limit the efficacy of current BTK inhibitors[6]
- In preclinical models, BGB-16673 degraded both wild-type BTK and mutant forms of BTK that have shown resistance to covalent and noncovalent BTK inhibitors; additionally, BGB-16673 showed central nervous system penetration[5,8]
- In a clinical study, BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[9]
- In the CaDAnCe-101 study (BGB-16673-101; NCT05006716), BGB-16673 monotherapy was well tolerated and demonstrated antitumor activity in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), follicular lymphoma (FL), and marginal zone lymphoma (MZL)[10-12]
- This presentation outlines the study design of CaDAnCe-104 (BGB-16673-104; NCT06634589), an ongoing phase 1b/2 trial to evaluate the safety and efficacy of BGB-16673 in combination with other agents in patients with selected relapsed/refractory B-cell malignancies

STUDY STATUS

- Enrollment for CaDAnCe-104 phase 1 began in November 2024, and the trial is currently recruiting
- This study has 50 locations across the US, Australia, Brazil, China, Germany, Italy, New Zealand, and Poland (**Figure 1**), with an estimated enrollment of 330 patients in phase 1

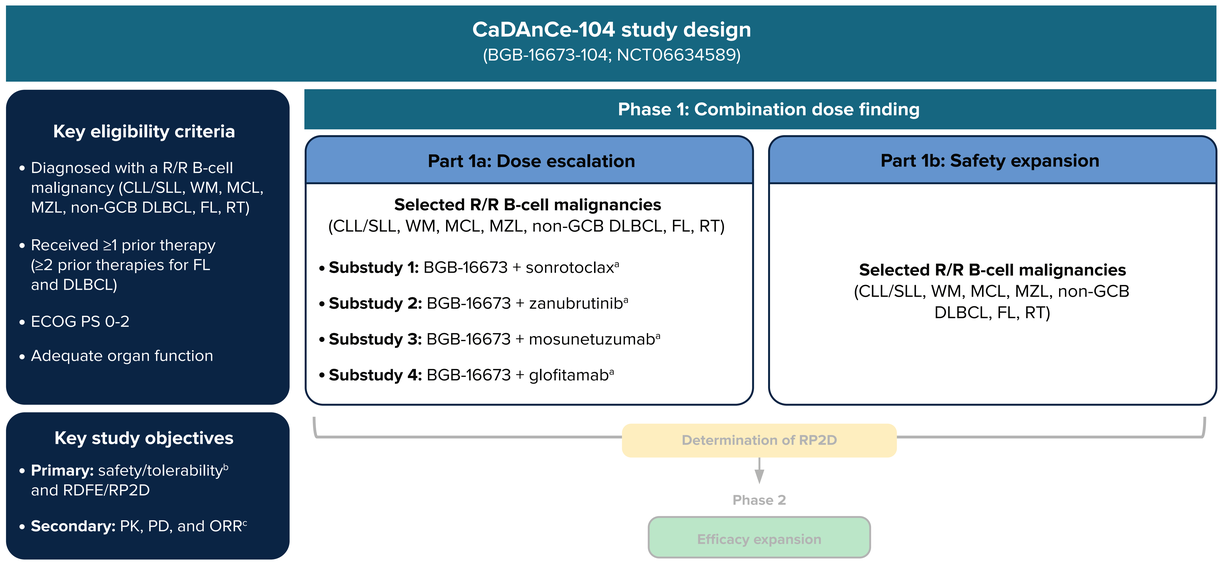
Figure 1. CaDAnCe-104 Study Sites (Planned)



METHODS

- CaDAnCe-104 (BGB-16673-104; NCT06634589) is a phase 1b/2, open-label, master protocol study comprising four substudies investigating the safety and effectiveness of BGB-16673 in combination with sonrotoclax, zanubrutinib, mosunetuzumab, or glofitamab in patients with selected relapsed/refractory B-cell malignancies, including CLL/SLL, WM, mantle cell lymphoma (MCL), MZL, non–germinal center B–cell like diffuse large B-cell lymphoma (non-GCB DLBCL), FL, and Richter transformation (RT) (**Figure 2**)
  - The primary objectives are to evaluate safety and tolerability per NCI-CTCAE v5.0 and to identify the recommended dose for expansion (RDFE) in part 1a and the recommended phase 2 dose in part 1b
  - The secondary objectives are to assess overall response rate, duration of response, and time to response at each dose level in part 1a and at the selected RDFE(s) and to assess the pharmacokinetics of BGB-16673 and combination drugs in their respective substudies
  - In addition, exploratory analyses will be conducted using patient samples to assess predictive, prognostic, and pharmacodynamic biomarkers

Figure 2. CaDAnCe-104 Study Design



[a]Treatment will be administered until progressive disease, unacceptable toxicity, withdrawal of consent, or other criteria are met for treatment discontinuation. [b]Safety will be assessed according to NCI-CTCAE v5.0 in all patients. [c]Response will be assessed per Lugano criteria for SLL, DLBCL, FL, RT, MZL, and MCL; iwCLL 2018 criteria for CLL; and IWWM-11 criteria for WM.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B-cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IWWM, Internal Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; RDFE, recommended dose for expansion; RP2D, recommended phase 2 dose; RT, Richter transformation; WM, Waldenström macroglobulinemia.

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