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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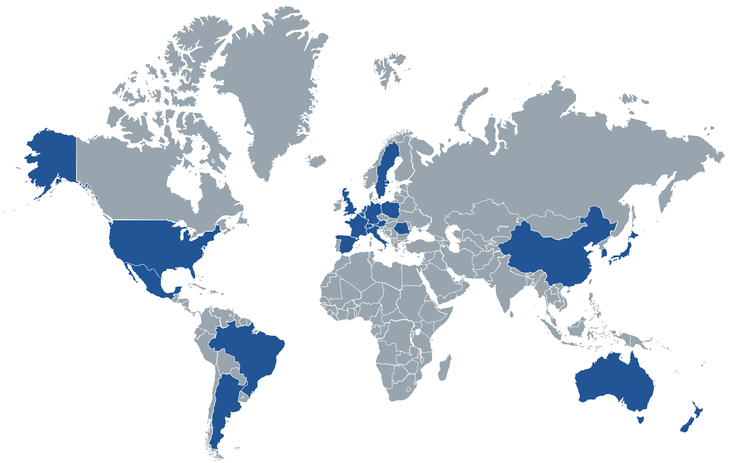
INTRODUCTION

- Targeting Bruton tyrosine kinase (BTK) has revolutionized the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1]
- Pirtobrutinib, a noncovalent BTK inhibitor, was recently approved for patients whose disease relapsed following covalent BTK inhibitor therapy such as ibrutinib, acalabrutinib, or zanubrutinib[2]
- 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[3]
- 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[4,5]
- 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[4]
- 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[3,6]
- In a clinical study, BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[7]
- Data from CaDAnCe-101 (BGB-16673-101; NCT05006716), an ongoing phase 1/2 study, demonstrated 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[8]
- Here, the study design of CaDAnCe-304 (BGB-16673-304; NCT06973187), an ongoing phase 3 trial in R/R CLL/SLL, is described

STUDY STATUS

- Enrollment for CaDAnCe-304 began in October 2025, and the study is currently recruiting
- Approximately 207 study sites in 23 countries are planned (**Figure 1**), with an estimated enrollment of 500 patients

Figure 1. CaDAnCe-304 Study Sites (Planned)



METHODS

- CaDAnCe-304 (BGB-16673-304; NCT06973187) is an open-label, randomized, phase 3 clinical study comparing the efficacy and safety of BGB-16673 vs pirtobrutinib in patients with R/R CLL/SLL previously treated with a covalent BTK inhibitor (**Figure 2**)

Figure 2. CaDAnCe-304 Study Design

Key eligibility criteria

- Age ≥18 years
- Confirmed CLL/SLL (iwCLL 2018 criteria)[9]
- R/R to ≥1 LOT[a] including a cBTKi
- Measurable disease by CT/MRI (SLL)
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK protein degraders or ncBTKi

Study design

R/R CLL/SLL with ≥1 prior LOT including cBTKi (N≈500)

R 1:1

Arm A: BGB-16673 (n≈250) Oral QD[b]

Arm B: Pirtobrutinib (n≈250) Oral QD[b]

Randomization stratified by:

- Prior BCL2i
- del(17p) and/or *TP53* mutated
- Refractory to last cBTKi treatment

Objectives

Primary

- PFS (IRC)[c]

Secondary

- OS
- PFS (INV)[c]
- ORR (IRC/INV)
- PR-L or better rate (IRC/INV)
- DOR (IRC/INV)
- Time to next treatment
- Safety/tolerability[d]
- PROs

[a]Defined as ≥2 consecutive cycles of systemic anticancer regimen. [b]Treatment continued until progressive disease or unacceptable toxicity. [c]Per modified 2018 iwCLL criteria[9] with modification for treatment-related lymphocytosis[10] for CLL and Lugano classification[11] for SLL. [d]Per NCI-CTCAE v5.0.

Abbreviations: BCL2i, B-cell lymphoma-2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; CLL, chronic lymphocytic leukemia; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LOT, line of therapy; MRI, magnetic resonance imaging; ncBTKi, noncovalent BTK inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR-L, partial response with lymphocytosis; PRO, patient-reported outcome; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

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