BGB-16673 versus idelalisib + rituximab (R), bendamustine + R, or venetoclax + R re-treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: the phase 3 CaDAnCe-302 trial

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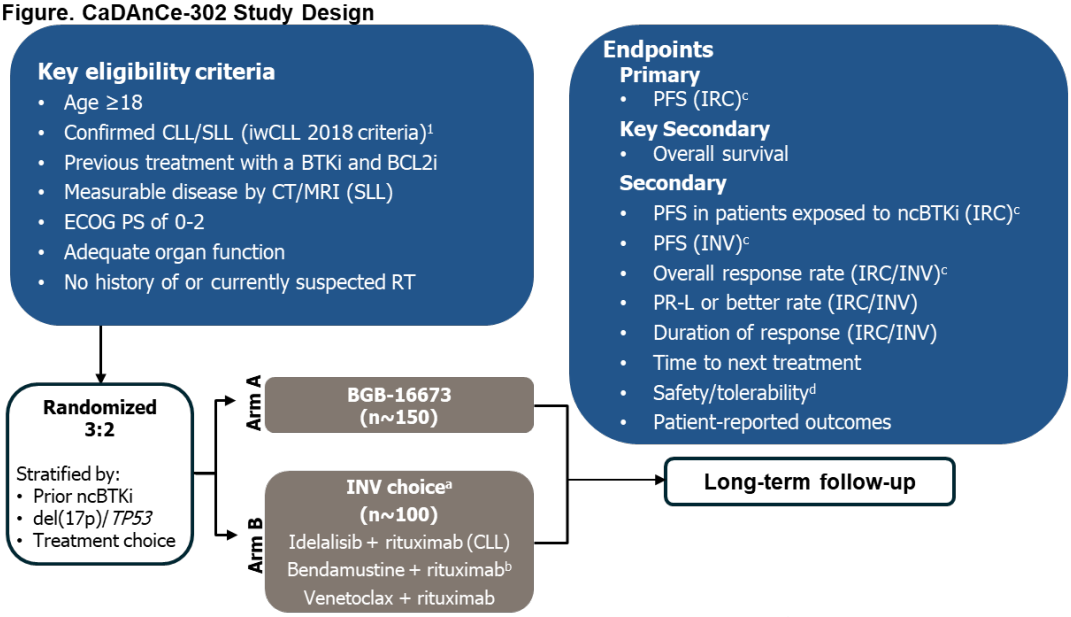
Background: Novel therapies, including Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors (BCL2is), have meaningfully improved patient outcomes in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, CLL/SLL remains incurable, and most patients will experience disease relapse following a BTKi or BCL2i. BGB-16673 is a BTK degrader that blocks 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, demonstrate 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 BTKi treatment and BTK resistance mutations. Here, CaDAnCe-302, an ongoing phase 3 study that will evaluate the efficacy and safety of BGB-16673 monotherapy vs investigator's choice (IC; idelalisib + rituximab [R], bendamustine + R, or venetoclax + R re-treatment) in patients with CLL/SLL previously exposed to BTK and BCL2 inhibitors, is described.

Methods: CaDAnCe-302 (BGB-16673-302, NCT06846671) is a global, open-label, randomized, phase 3 clinical study (Figure) conducted across approximately 137 sites in 14 countries. Eligible patients are ≥18 years of age with a confirmed diagnosis of CLL/SLL that has relapsed after treatment with a covalent BTKi and a BCL2i or is refractory to these treatments. Prior treatment with a noncovalent BTKi is also required in regions where they are approved and available. Patients are excluded if they have prolymphocytic leukemia or history of, or currently suspected, Richter transformation, have received an autologous stem cell transplant or chimeric antigen receptor T-cell therapy in the last 3 months, or had prior exposure to any BTK protein degraders. Approximately 250 patients are planned to be enrolled and randomized 3:2 to receive either BGB-16673 once daily (arm A) or IC of idelalisib + R (for CLL only), bendamustine + R [for CLL/SLL without del(17p) or *TP53* mutation], or venetoclax + R re-treatment (arm B) until disease progression or intolerance. For patients to be considered for venetoclax + R re-treatment, the best overall response of the last BCL2i-

based regimen should be partial response or better, with the last BCL2i dose being ≥1 year prior to the most recent disease progression, and the patient should have been able to tolerate previous BCL2i treatment. Patients in arm B will be given the option to cross over to BGB-16673 treatment after confirmation of progressive disease by both the investigator and independent review committee (IRC). The primary endpoint is progression-free survival (PFS), as determined by IRC per modified 2018 International Workshop on CLL criteria (for CLL) or Lugano classification (for SLL). Overall survival is the key secondary endpoint; additional secondary endpoints include PFS in patients with prior exposure to noncovalent BTKis by IRC, PFS by investigator, overall response rate by IRC and investigator, rate of partial response with lymphocytosis or higher by IRC and investigator, duration of response by IRC and investigator, time to next treatment, and safety/tolerability per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Recruitment is ongoing.

Image/Table (Limit 1):

Figure. CaDAnCe-302 Study Design



[a]Patients have the option to crossover to BGB-16673 treatment after INV and IRC confirmation of progressive disease. [b]CLL/SLL without del(17p)/ *TP53* mutation. [c]Per modified 2018 iwCLL criteria[1] for CLL and Lugano classification[2] for SLL. [d]Per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.
Abbreviations: BCL2i, B-cell lymphoma-2 inhibitor; BTK, Bruton tyrosine kinase; BTK, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; ncBTKi, noncovalent BTK inhibitor; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; RT, Richter transformation.
1. Hallek M, et al. *Blood.* 2018;131(25):2745-60. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-68.