CLL-415

Phase 3 BELLWAVE-010: Nemtabrutinib Plus Venetoclax Versus Venetoclax Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Background

- Venetoclax plus rituximab (VR) is a standard therapy among patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who experienced a relapse after ≥1 line of prior therapy[1]; however, there is an unmet need for more effective treatments
- Bruton tyrosine kinase (BTK) is a critical signaling molecule in the pathogenesis of CLL, and treatment with BTK inhibitors (BTKis) resulted in significant improvements in survival for patients with CLL[2]
- Nemtabrutinib is a noncovalent, reversible, competitive BTKi that does not require the C481 residue of BTK for the binding and inhibition of kinase activity[3]; as a result, nemtabrutinib can target both the wild-type and C481-mutant forms of BTK
- Results from the ongoing BELLWAVE-001 study have demonstrated manageable safety and durable antitumor activity of nemtabrutinib in patients with CLL/SLL with and without C481 mutations[4]
- The active-controlled, open-label, randomized, phase 3 BELLWAVE-010 study (NCT05947851) is designed to investigate the efficacy and safety of nemtabrutinib plus venetoclax versus VR as second-line (2L) or later treatment for patients with relapsed or refractory (R/R) CLL/SLL
  - This study will consist of 2 parts: a nonrandomized dose escalation and confirmation phase (part 1) and a parallel-group randomized phase comparing the efficacy and safety of nemtabrutinib plus venetoclax with VR (part 2)

Objectives

Primary

- Part 1
  - To evaluate the safety and tolerability, including dose-limiting toxicities, and establish the recommended dose of nemtabrutinib plus venetoclax
- Part 2
  - To compare progression-free survival (PFS) per International Working Group for Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria by blinded independent central review (BICR) of nemtabrutinib plus venetoclax versus VR

Secondary

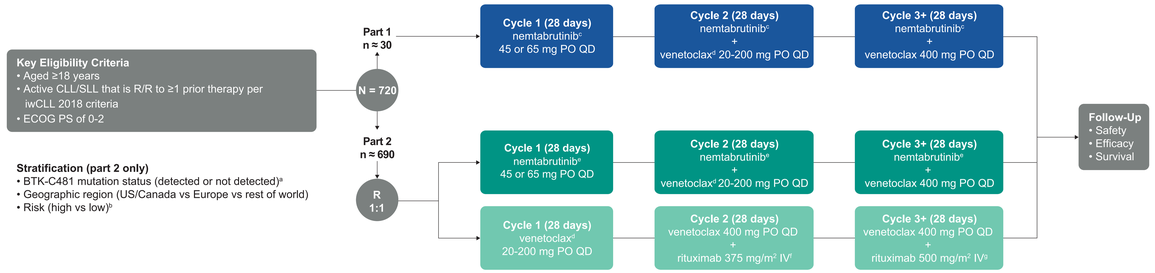
- Part 2
  - To compare the following for nemtabrutinib plus venetoclax versus VR
    - Undetectable minimal residual disease rate in bone marrow at month 14 as assessed by central laboratory
    - Objective response rate (ORR) per iwCLL 2018 criteria by BICR
    - Overall survival (OS)
  - To evaluate duration of response per iwCLL 2018 criteria by BICR of nemtabrutinib plus venetoclax and VR
  - To evaluate safety and tolerability of nemtabrutinib plus venetoclax

Exploratory

- Part 2
  - To evaluate the following for nemtabrutinib plus venetoclax and VR
    - ORR including partial response with lymphocytosis per iwCLL 2018 criteria by BICR
    - Health-related quality of life
  - To characterize the pharmacokinetics of nemtabrutinib

Methods

Study design



ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; PO, by mouth; QD, once daily, R, randomization.
[a]Determined by droplet digital polymerase chain reaction with a limit of detection of approximately 0.01% to 0.1%.
[b]High risk is defined as del(17p) and/or *TP53*-mutated and/or *IGHV*-unmutated, and low risk is defined as the absence of high-risk factors.
[c]Dose escalation and confirmation will follow the modified toxicity probability interval design with approximately 15 patients per dose level.
[d]Ramp-up over 4 weeks.
[e]Dose selection from part 1.
[f]Patients will receive rituximab (or a rituximab biosimilar) as an intravenous infusion at week 6.
[g]Patients will receive rituximab (or a rituximab biosimilar) as an intravenous infusion every 28 days starting at week 10 until week 26 (total of 6 doses).

Patient eligibility

Key inclusion criteria	Key exclusion criteria
• Aged ≥18 years • Confirmed diagnosis of CLL/SLL and active disease, with a clearly documented need to initiate therapy • CLL/SLL relapsed or refractory to ≥1 prior available therapy per iwCLL 2018 criteria • ECOG PS of 0 to 2 • Deletion 17p status, *TP53* mutation status, *IGHV* mutation status, and BTK-C481 mutation status, as determined by central testing, required before randomization for part 2 participants only • Have ≥1 marker of disease burden: – Malignant lymph nodes with longest diameter >1.5 cm – Absolute lymphocyte count >4 × 10^9/L – Platelet count <100 × 10^9/L – Hemoglobin <11 g/dL • Life expectancy of ≥3 months • Adequate organ function	• Active HBV/HCV infection[a] • Received prior BCL2i (including venetoclax) or noncovalent BTKi therapy • Diagnosis of Richter transformation • Active central nervous system involvement • Known additional malignancy • History of severe bleeding disorder • Active infection requiring systemic therapy • Prior systemic anticancer therapy ≤4 weeks before randomization • Received a live or live attenuated vaccine ≤30 days before the first dose of study intervention • Prior treatment with an investigational agent ≤4 weeks before study intervention • Infection with HIV and a history of Kaposi sarcoma and/or multicentric Castleman disease and/or AIDS-defining opportunistic infection in the past 12 months before screening[b] • Currently being treated with P-gp substrates with a narrow therapy index or CYP3A inducers (strong or moderate)

BCL2i, B-cell lymphoma 2 inhibitor; CYP3A, cytochrome P450 3A; HBV, hepatitis B virus; HCV, hepatitis C virus; P-gp, p-glycoprotein.
[a]Patients infected with HBV/HCV are eligible if they have received HBV/HCV antiviral therapy for ≥4 weeks and have undetectable HBV DNA or HCV RNA viral load before randomization.
[b]Patients infected with HIV are eligible if they have a CD4 count of ≥350 cells/μL at screening, achieved and maintained virologic suppression, defined as confirmed HIV RNA level below 50 or the lower limit of quantitation (below the limit of detection), per the locally available assay at the time of screening and for ≥12 weeks before screening; are on a stable antiretroviral therapy regimen for ≥4 weeks before study entry; and are adherent to their antiretroviral therapy.

Assessment and follow-up

Assessment	Detail
Tumor response	• Treatment response assessment, including computed tomography imaging, until progression • Response assessments (including imaging, physical examination, constitutional symptoms, hematological evaluations, and bone marrow) will be performed at 12 weeks from the date of randomization, then every 12 weeks up to week 97 (~2 years), and then every 24 weeks thereafter or until any criteria for discontinuation are met
AEs	• AEs will be monitored from time of randomization through 30 days after cessation of treatment (90 days for serious AEs) • Severity will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 • Hematologic toxicity will be assessed per iwCLL 2018 criteria
PROs	• PROs will be assessed using the EORTC QLQ-C30, EORTC QLQ-CLL17, and EuroQol EQ-5D-5L

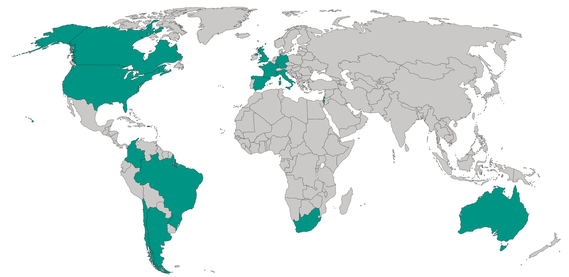
AE, adverse event; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; EORTC QLQ-CLL17, EORTC Quality of Life Questionnaire Chronic Lymphocytic Leukemia module 17; EuroQol EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; PRO, patient-reported outcome.

Analyses

Analysis	Detail
Efficacy	• Part 2 only – Efficacy will be assessed in all randomly assigned patients (intent-to-treat population) – Treatment differences for PFS and OS will be assessed by a stratified log-rank test. Hazard ratios and 95% CIs will be estimated using a stratified Cox regression model with the Efron method of tie handling – PFS and OS will be estimated using the Kaplan-Meier method – ORR and undetected minimal residual disease will be evaluated using the stratified Miettinen and Nurminen method with strata weighted by sample size
Safety	• Safety will be assessed in all randomly assigned patients who received ≥1 dose of study treatment (all-patients-as-treated population) • AEs will be summarized descriptively • The Miettinen and Nurminen method will be used for between-treatment differences in the percentage of patients with events
PROs	• PROs will be assessed in all randomly assigned patients who have ≥1 PRO assessment available for the specific end point and have received ≥1 dose study treatment

Status

Sites of patient enrollment for BELLWAVE-010 (green)



References

1. Seymour JF et al. *N Engl J Med.* 2018;378:1107-1120.
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