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Sonrotoclax (BGB-11417) Plus Zanubrutinib vs Venetoclax Plus Acalabrutinib in Treatment-Naive Chronic Lymphocytic Leukemia: A Phase 3 Randomized Trial Design (CELESTIAL-TNCLL-2)

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INTRODUCTION

- Inhibition of B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) has emerged as an effective fixed-duration treatment strategy for patients with treatment-naive chronic lymphocytic leukemia (TN CLL)[1]
- Venetoclax + acalabrutinib is approved in the US and EU as a first-line fixed-duration treatment for TN CLL[2,3]
- Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation[4,5]
- Zanubrutinib is a highly potent next-generation BTK inhibitor approved in the US and EU for the treatment of CLL/small lymphocytic lymphoma[6,7]
- In the ongoing phase 1/1b study BGB-11417-101 (NCT04277637), sonrotoclax + zanubrutinib demonstrated promising efficacy and a favorable safety profile in patients with TN CLL, including those with high-risk features[8]
  - In 135 evaluable patients, the overall response rate was 100% and the complete response rate was 56%
  - Undetectable minimal residual disease rates at 10^{-4} sensitivity (uMRD4; among intention-to-treat population who reached week 96) increased over time, with 98% (55/56) of patients in the sonrotoclax 320-mg cohort achieving uMRD4 by 96 weeks
  - Sonrotoclax + zanubrutinib was generally well tolerated, with predominantly grade 1 or 2 treatment-emergent adverse events (TEAEs), a low sonrotoclax discontinuation rate due to TEAEs, and no cases of tumor lysis syndrome
- These promising results support further evaluation of sonrotoclax + zanubrutinib in TN CLL

METHODS

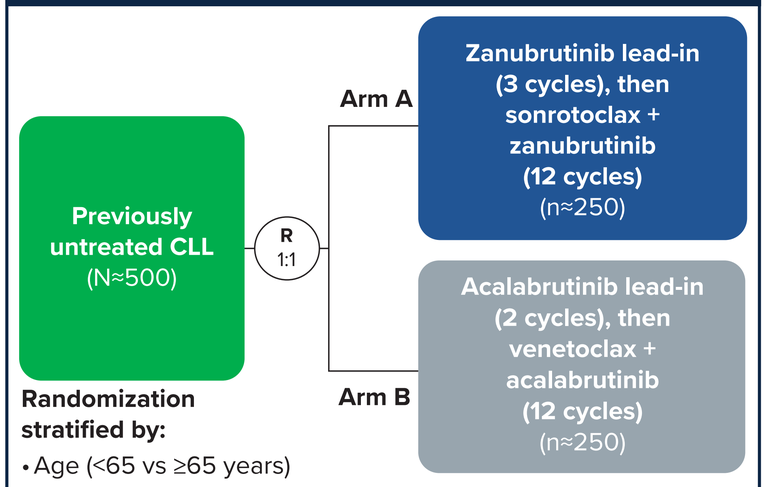
- CELESTIAL-TNCLL-2 (BGB-11417-304; NCT07277231) is a phase 3, global, open-label, randomized study of fixed-duration sonrotoclax + zanubrutinib (arm A) vs venetoclax + acalabrutinib (arm B) in adults with TN CLL (**Figure 1**)
- Approximately 500 patients will be randomized 1:1 to:
  - Arm A: 3 cycles of zanubrutinib lead-in, then 12 cycles of sonrotoclax + zanubrutinib
  - Arm B: 2 cycles of acalabrutinib lead-in, then 12 cycles of venetoclax + acalabrutinib
- The primary endpoint is progression-free survival assessed by independent review committee in arm A vs arm B, with an intermediate endpoint of uMRD4 rate in blood and bone marrow per next-generation sequencing in arm A vs arm B

Figure 1. CELESTIAL-TNCLL-2 Study Design

Key eligibility criteria

- Age ≥18 years
- Confirmed diagnosis of CLL requiring treatment per iwCLL 2018 criteria[9]
- Measurable disease by CT/MRI
- ECOG PS of 0-2
- Adequate BM and organ function
- No known PLL or history of/currently suspected RT
- No known CNS involvement
- No uncontrolled hypertension or clinically significant CVD

Study design



Randomization stratified by:

- Age (<65 vs ≥65 years)
- IGHV (mutated vs unmutated)
- del(17p)/*TP53* mutation (both absent vs ≥1 present)

ClinicalTrials.gov: NCT07277231

Endpoints

Primary
- PFS (IRC)

Intermediate
- uMRD4 rate in BM and PB

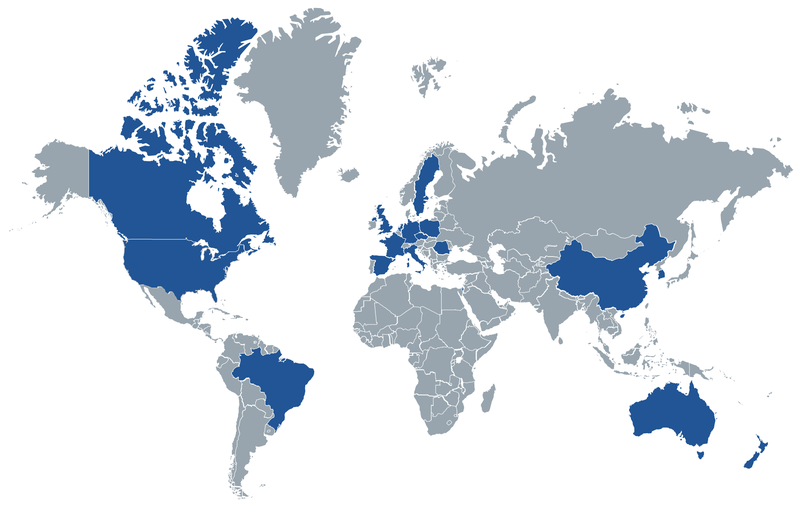
Key secondary
- PFS (IRC) in high-risk subgroups[a]
- OS

Other secondary
- ORR (IRC and INV)
- CRR[b] (IRC and INV)
- uMRD5 rate in BM and PB
- PFS (INV)
- DOR (IRC and INV)
- Time to next treatment
- Patient-reported outcomes
- Safety and tolerability

STUDY STATUS

- CELESTIAL-TNCLL-2 enrollment began in January 2026, and the study is currently recruiting
- Approximately 122 study sites are planned across Europe, the Americas (ie, US, Canada, and Latin America), and the Asia-Pacific region (**Figure 2**)

Figure 2. CELESTIAL-TNCLL-2 Study Sites



[a]Patients with unmutated IGHV and/or *TP53* aberrations (del(17p) present and/or *TP53* mutated). [b]Defined as the proportion of patients with CR or CR with incomplete recovery.
Abbreviations: BM, bone marrow; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CR, complete response; CRR, complete response rate; CT, computed tomography; CVD, cardiovascular disease; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; INV, investigator; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PLL, prolymphocytic leukemia; R, randomized; RT, Richter transformation; uMRD4 or 5, undetectable minimal residual disease at 10^{-4} or 10^{-5} sensitivity.

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DISCLOSURES

MS: Consulting, advisory boards, steering committees, or data safety monitoring committees: AbbVie, Ascentage, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines, Ltd, BMS, Morphosys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck, Pfizer, Pierre Fabre; Research funding: Genentech, BeOne Medicines, Ltd, AstraZeneca, Genmab, Morphosys/Incyte, Sana Biotechnology, Nurix, Merck, Janssen; Employment (spouse): BMS; Stock options: Koi Biotherapeutics.

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