Sonrotoclax (BGB-11417) + zanubrutinib vs venetoclax + acalabrutinib in treatment-naive chronic lymphocytic leukemia: A phase 3 randomized trial design (CELESTIAL-TNCLL-2)

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Background: Inhibition of B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) has emerged as an effective fixed-duration treatment strategy that can induce high rates of undetectable minimal residual disease (uMRD) in patients with treatment-naive chronic lymphocytic leukemia (TN CLL). Venetoclax + acalabrutinib (AV) is approved in the EU as a first-line fixed-duration treatment for TN CLL. 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. Zanubrutinib is a highly potent next-generation BTK inhibitor that is approved in the US and EU for CLL. In an ongoing phase 1/1b trial (NCT04277637), sonrotoclax + zanubrutinib (SZ) has had promising efficacy, with a 100% overall response rate (ORR; n=135) and high rates of blood uMRD at 10^{-4} sensitivity (uMRD4) in patients with TN CLL, including those with high-risk disease features. SZ is generally well tolerated, with neutropenia as the most common grade ≥3 treatment-emergent adverse event and no laboratory or clinical tumor lysis syndrome events occurred.

Aims: The phase 3 trial BGB-11417-304 (NCT07277231) was designed to directly compare fixed-duration SZ vs AV in TN CLL to investigate whether SZ compared with AV, may improve efficacy as assessed by uMRD rate after treatment completion and progression-free survival (PFS) and potentially improve tolerability and safety.

Methods: BGB-11417-304 is a global phase 3, open-label, randomized study. Eligible adults have a confirmed diagnosis of previously untreated CLL requiring treatment per iwCLL 2018 criteria, adequate hematologic and organ function, an ECOG PS of 0-2, and measurable disease confirmed by CT or MRI. Exclusion criteria include prior systemic treatment for CLL; diagnosis of prolymphocytic leukemia or Richter transformation; known central nervous system involvement; history of confirmed progressive multifocal leukoencephalopathy; or uncontrolled hypertension or clinically significant cardiovascular disease. Approximately 500 patients will be enrolled and randomized 1:1 to arm A (3 lead-in cycles of oral zanubrutinib monotherapy followed by 12 cycles of oral SZ) or arm B (2 lead-in cycles of oral acalabrutinib monotherapy followed by 12 cycles of oral AV). Randomization will be stratified by age (<65 years vs ≥65 years), IGHV mutation status, and presence of del(17p) and/or *TP53* mutations. The primary endpoint is PFS in arm A vs arm B, as determined by independent review committee (IRC), with an intermediate endpoint of uMRD4 rate in blood and bone marrow in arm A vs arm B, assessed by next-generation sequencing (clonoSEQ) at the first post-treatment follow-up visit.

Key secondary endpoints are PFS-IRC in high-risk subgroups and overall survival (OS). Other secondary endpoints are ORR and complete response assessed by IRC and investigator (INV), uMRD5 rate (clonoSEQ), PFS-INV, duration of response by IRC and INV, time to next treatment, patient-reported outcomes, and safety/tolerability. Enrollment in BGB-11417-304 is currently ongoing.