American Society of Clinical Oncology (ASCO)
May 29 - June 2, 2026, Chicago, IL & Online

Sonrotoclax (BGB-11417) + zanubrutinib (SZ) vs venetoclax + acalabrutinib (AV) in treatment-naive chronic lymphocytic leukemia (TN CLL): 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 (tx) strategy that can induce high rates of undetectable minimal residual disease (uMRD) in patients (pts) with TN CLL. AV is approved in the EU as a first-line fixed-duration tx 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/EU for CLL. In an ongoing phase 1/1b trial (NCT04277637), SZ has had promising efficacy, with a 100% ORR (n=135) and high rates of blood uMRD at 10^{-4} sensitivity (uMRD4) in pts with TN CLL, including those with high-risk disease features. SZ is generally well tolerated, with neutropenia as the most common grade ≥3 TEAE and no laboratory or clinical TLS events occurred. 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 in terms of achieved uMRD rate after completing treatment and 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 tx per iwCLL 2018 criteria, adequate hematologic and organ function, ECOG PS 0-2, and measurable disease confirmed by CT/MRI. Exclusion criteria include prior systemic tx 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 pts 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 y vs ≥65 y), 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-tx follow-up visit. Key secondary endpoints are PFS-IRC in high-risk subgroups and 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 tx, pt-reported outcomes, and safety/tolerability. Enrollment in BGB-11417-304 is currently ongoing.