CELESTIAL-TNCLL: An ongoing, open-label, multiregional, phase 3 study of sonrotoclax (BGB-11417) + zanubrutinib vs venetoclax + obinutuzumab in treatment-naive CLL

Authors: A. Cuneo[1], P.E.M. Patten[2|3], A.P. Kater[4], J.A. Woyach[5], J. Li[6], T. Munir[7], T. Salmi[8], P. Phuong[9], T. Tian[9], M. Shadman[10|11]

Affiliations: [1]Hematology Section, St. Anna University Hospital, [2]Comprehensive Cancer Centre, King's College London; [3]King's College Hospital; [4]Lymphoma and Myeloma Research Amsterdam; [5]Ohio State University Comprehensive Cancer Center; [6]The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital; [7]Leeds Teaching Hospitals NHS Trust; [8]BeiGene International GmbH; [9]BeiGene USA, Inc; [10]Fred Hutchinson Cancer Research Center; [11]University of Washington

ABSTRACT

Background: The combination of venetoclax (ven), the first-generation BCL2 inhibitor, and ibrutinib, a BTK inhibitor, has efficacy in CLL. However, the toxicity profile of this regimen suggests a need for a more tolerable combination of BTK and BCL2 inhibitors. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than ven in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor, significantly improved progression-free survival (PFS) and had a more tolerable safety profile, including fewer cardiac adverse events, vs ibrutinib in a randomized head-to-head study in patients with CLL/SLL. In a phase 1 study in patients with treatment-naive (TN) CLL treated with sonrotoclax + zanubrutinib, the ORR and 1-year PFS rate were 100%, and deep responses based on undetectable measurable residual disease at $<10^{-4}$ sensitivity (uMRD4) were observed. The most common grade ≥3 TEAE was neutropenia, and no tumor lysis syndrome or cardiac toxicity was observed. The design of a phase 3 trial to compare the efficacy of sonrotoclax + zanubrutinib vs ven + obinutuzumab (obi) in patients with TN CLL is presented.

Methods: CELESTIAL-TNCLL (BGB-11417-301; NCT06073821) is a randomized, open-label, phase 3 study. Eligible patients have previously untreated CLL that requires treatment per 2018 iwCLL criteria, measurable disease by CT/MRI, an ECOG performance status of 0 to 2, and adequate hematologic and organ function. Approximately 640 patients will be randomized 1:1 to receive either 3 cycles of oral zanubrutinib monotherapy (320 mg daily) followed by zanubrutinib + sonrotoclax or standard ven + obi for 12 cycles. Randomization will be stratified by age (<65 vs ≥65 years) and IGHV and del(17p)/*TP53* mutation status. The primary endpoint is PFS assessed by independent review committee (IRC) per 2018 iwCLL guidelines, with modifications for treatment-related lymphocytosis in patients with CLL. Key secondary endpoints include complete response rate (CRR), defined as CR or CR with incomplete hematopoietic recovery, assessed by IRC; rates of uMRD4 in bone marrow and peripheral blood at the first post-treatment follow-up visit by next-generation sequencing (clonoSEQ®); and overall survival. Other secondary endpoints include investigator (INV)-assessed PFS, CRR-INV, uMRD4 rate by flow cytometry, ORR-IRC and -INV, DOR-IRC and -INV, patient-reported outcomes, and safety and tolerability. Recruitment is ongoing.