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

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Introduction: The combination of venetoclax, the first-generation BCL2 inhibitor, and ibrutinib, a BTK inhibitor, has demonstrated efficacy in patients with chronic lymphocytic leukemia (CLL) (Wierda et al. *J Clin Oncol.* 2021); however, the toxicity profile of this regimen suggests a need for a more tolerable BTK/BCL2 inhibitor combination. Sonrotoclax, a next generation BCL2 inhibitor, is a more selective and more pharmacologically potent inhibitor of BCL2 than venetoclax. In a phase 1 study in patients with treatment-naive (TN) CLL treated with sonrotoclax + zanubrutinib, efficacy data was promising with ORR and 1-year progression-free survival (PFS) rates of 100% and deep responses based on undetectable measurable residual disease at $<10^{-4}$ sensitivity (uMRD4). The most common grade ≥3 TEAE was neutropenia, and no tumor lysis syndrome or cardiac toxicity was observed. Zanubrutinib, a next-generation BTK inhibitor, significantly improved PFS and had a more tolerable safety profile, including fewer cardiac adverse events vs ibrutinib in a randomized, head-to-head study of patients with CLL/small lymphocytic lymphoma (SLL). Presented here is the design of a phase 3 trial aimed at comparing the efficacy of sonrotoclax + zanubrutinib vs venetoclax + obinutuzumab in patients with TN CLL.

Methods: CELESTIAL-TNCLL (BGB-11417-301; NCT06073821) is a randomized, open-label, phase 3 study. Eligible patients must have previously untreated CLL that requires treatment per 2018 iwCLL criteria, measurable disease by CT/MRI, an ECOG performance score of 0-2, and adequate hematologic and organ function. Approximately 640 patients will be randomized 1:1 to receive either 3 cycles of zanubrutinib monotherapy (320 mg total daily dose, orally), followed by zanubrutinib + sonrotoclax for 12 cycles, or standard venetoclax + obinutuzumab treatment 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 as assessed by independent review committee (IRC) according to 2018 iwCLL guidelines with modifications for treatment-related lymphocytosis for 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 based on next-generation sequencing by clonoSEQ®; and overall survival. Other secondary endpoints include PFS as assessed by investigator (INV); CRR by INV; rate of uMRD4 based on flow cytometry; overall response rate by IRC and INV; duration of response by IRC and INV; patient-reported outcomes; and safety and tolerability. Recruitment is ongoing at approximately 230 study sites in 20 countries, including 50 sites in the US, 6 in Brazil, and 15 in Canada.