Title: Phase 3 Zanubrutinib (BGB-3111) vs Bendamustine + Rituximab (BR) in Patients (pts) with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Authors: Jennifer R Brown, MD, PhD,[1] Brad Kahl, MD,[2] Paolo Ghia, MD, PhD,[3] Tadeusz Robak, MD, PhD,[4] Constantine Tam, MD,[5] Carol Marimpietri,[6] Aileen Cohen, MD, PhD,[6] Jane Huang, MD,[6] and Peter Hillmen, MD, PhD[7]

Affiliations: [1]Dana Farber Cancer Institute, Boston, MA, USA; [2]Washington University School of Medicine, St Louis; MO, USA; [3]Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milano, Italy; [4]Medical University of Lodz, Lodz, Poland; [5]St. Vincent's Hospital, Melbourne, Melbourne, Victoria, Australia; [6]BeiGene, San Mateo, CA, USA; [7]The Leeds Teaching Hospitals, St. James University Hospital, Leeds, UK.

Introduction: Inhibition of Bruton's tyrosine kinase (BTK) has emerged as a strategy for targeting B-cell malignancies including CLL/SLL. Zanubrutinib has been shown to be a novel 2nd-generation, potent, and specific BTK inhibitor in clinical studies to date. Early clinical data suggest that zanubrutinib treatment in pts with TN (n = 16) or relapsed/refractory (R/R; n = 50) CLL/SLL induced deep and sustained responses, with a 94% overall response rate (ORR) including 6% and 2% complete response rates in TN and R/R CLL/SLL, respectively (ICML 2017). We hypothesize that zanubrutinib monotherapy may have superior efficacy and potentially improved safety vs standard BR chemoimmunotherapy in pts with TN CLL/SLL.

Methods*:* This ongoing Phase 3, randomized, open-label, global study (NCT03336333, BGB-3111-304) compares the efficacy and safety of zanubrutinib vs BR in adult pts with TN CLL/SLL considered unsuitable for treatment with FCR (fludarabine, cyclophosphamide, rituximab). In Cohort 1, pts lacking del(17p) (n ≈ 420) are randomized 1:1 to oral zanubrutinib 160 mg twice-daily or BR x 6 cycles. Randomization is stratified by age (< 65 vs ≥ 65 y), Binet stage (C vs A/B), geographic region (North America vs Europe vs Asia-Pacific) and *IGHV* mutational status (mutated vs unmutated). In Cohort 2, pts with del(17p) (n ≈ 47) are enrolled and all receive zanubrutinib as in Cohort 1. Key inclusion criteria include histologically confirmed CD20+ CLL/SLL requiring treatment per iwCLL criteria, ECOG PS 0-2, and adequate hematologic function. The primary endpoint is progression-free survival (PFS) of zanubrutinib as compared to BR in Cohort 1 by independent review committee (IRC) according to iwCLL guidelines with modification for treatment-related lymphocytosis. The analysis of PFS between the 2 arms in Cohort 1 will be based on a log-rank test stratified by the randomization stratification factors. Key secondary end points include ORR, duration of response, overall survival, and safety in Cohorts 1 & 2. In Cohort 1, next-line treatment with zanubrutinib after IRC-confirmed progression on BR is included in the study design. Recruitment is ongoing.