A Head-to-Head Phase 3 Study Comparing BGB-3111 and Ibrutinib in Patients With Waldenström Macroglobulinemia

Authors:

Christian Buske, MD, Universitätsklinikum Ulm, Ulm, Germany; **Veronique LeBlond, MD,** Pitié Salpêtrière Hospital, Paris, France; **William Novotny, MD,** BeiGene; **Roger Owen, MD,** St James' University Hospital, Leeds, United Kingdom; **Alessandra Tedeschi, MD,** Niguarda Cancer Center Division of Hematology, Milan, Italy; **Siminder Atwal, PhD,** BeiGene; **Aileen Cohen, MD, PhD**, BeiGene; **Jane Huang, MD,** BeiGene; and **Constantine Tam, MD,** St. Vincent's Hospital, Melbourne, Melbourne, Victoria, Australia

Introduction: Bruton's tyrosine kinase (BTK) is a critical component of the B-cell receptor signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies including Waldenström macroglobulinemia (WM), particularly WM harboring the MYD88 mutation (*MYD88*^{MUT}). BGB-3111 is a novel second-generation, potent, specific, and irreversible BTK inhibitor. Preclinical data in cell lines and primary patient samples show specific and profound BTK inhibition, with minimal inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2, and TEC. Preliminary clinical data indicate that BGB-3111 treatment in patients with relapsed/refractory (R/R) WM induces deep and sustained responses, with a high (39%) very good partial response (VGPR) rate. Based on these encouraging results with a higher VGPR rate than previously reported for ibrutinib in R/R WM patients, we hypothesized that BGB-3111 achieves a more complete inhibition of BTK in lymph nodes with deeper tissue penetration than ibrutinib, resulting in improved efficacy and, based on its higher selectivity, a better safety profile for BGB-3111 than ibrutinib.
Methods*:* To test these hypotheses, we have designed a head-to-head, randomized, open-label, global phase 3 study to compare the efficacy and safety of BGB-3111 with those of ibrutinib in patients with R/R or treatment-naïve WM, the latter being unsuitable for treatment with standard chemoimmunotherapy. Approximately 150 *MYD88*^{MUT} WM patients in need of treatment will be enrolled into cohort 1 and randomized to 1 of 2 treatment arms (cohort 1; BGB-3111 160 mg orally twice daily [arm A] or ibrutinib 420 mg/d orally [arm B]) in a 1:1 ratio. Patients with wildtype *MYD88* (*MYD88*^{WT}), which is estimated to be present in approximately 10% of enrolled patients, will be enrolled into cohort 2 and will receive BGB-3111 160 mg orally twice daily on a third, nonrandomized study arm (arm C). The study schema is depicted in Figure 1. Patients will be treated until disease progression. Key eligibility criteria include age ≥18 years, histologically confirmed WM requiring treatment per the seventh International Workshop on WM,

Eastern Cooperative Oncology Group performance status of 0-2, and adequate hematologic function. The primary objective is to demonstrate superiority of BGB-3111 to ibrutinib in terms of the proportion of patients achieving complete response or VGPR, as determined by an independent review committee by modified Owens criteria (*Br J Haematol*. 2013;160:171 and National Comprehensive Cancer Network Guidelines). Key secondary end points include major response rate, duration of response, progression free survival, and safety. Study recruitment is ongoing, with the first patient enrolled in January 2017 and participating sites in Europe, Asia-Pacific, and North America (NCT03053440).