# Treatment with the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) Demonstrates High Overall Response Rate and Durable Responses in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Updated Results from a Phase 1/2 Trial

Gavin Cull, MB, BS, FRACP, FRCPA,David Simpson, MBChB, FRACP, FRCPA,Stephen Opat,
Jan A. Burger, MD PhD,Judith Trotman, MBChB, FRACP, FRCPA,
Paula Marlton, MBBS (Hons), FRACP, FRCPA,David Gottlieb, MBBS, MD FRACP, FRCPA,
Javier Munoz, MD MS, FACP,John F. Seymour, MBBS, PhD FRACP,Andrew W. Roberts, MBBS, PhD,
Ken Wu, PhD,Siminder Atwal, PhD,William Novotny, MD,Jane Huang, MD,Constantine S. Tam, MBBS, MD

**Background:** Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling. Inhibition of BTK has emerged as a strategy for targeting B-cell malignancies including CLL/SLL. Zanubrutinib (BGB-3111) is an investigational, next-generation BTK inhibitor, designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and

EGFR-family kinases. In non-clinical studies it has been shown to be highly potent, selective, bioavailable, and irreversible with potentially advantageous pharmacokinetic and pharmacodynamic properties. Zanubrutinib trials have allowed use of anticoagulant and antiplatelet agents, and co-administration with strong or moderate CYP3A inhibitors at a reduced dose; proton pump inhibitors or other gastric acid-reducing agents have not been shown to affect zanubrutinib exposure. Zanubrutinib has been shown to achieve complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes (Tam et al. *Blood* 2019), and preliminary data at median follow-up of 13.7 months indicated durable clinical responses in patients with CLL/SLL. Here, we present updated zanubrutinib safety and efficacy data in a larger cohort of these patients, with an additional 12 months of follow-up.

**Methods:** This is a global, open-label, multicenter, phase 1/2 study in patients with various B-cell malignancies with indication-specific expansion cohorts. Patients received doses of zanubrutinib ranging from 40 mg once daily to the final recommended phase 2 dose of 160 mg twice daily or 320 mg once daily until disease progression (PD) or unacceptable toxicity. We report here on the 122 patients with CLL/SLL with no prior BTK therapy. The primary endpoint was safety/tolerability. Secondary endpoints included response rate and progression-free survival (PFS).

**Results:** As of December 13, 2018, 117 patients with CLL and 5 patients with SLL had received zanubrutinib (Table 1). Twenty-two (18%) had received no prior therapy for CLL/SLL (median follow-up of 27.2 months [range, 11.1-42.8] in treatment-naïve patients). The most common (≥15%) adverse events (AEs) of any grade were contusion (46%; 41% grade 1), upper respiratory tract infection (39%), diarrhea (30%), cough (28%), headache (23%), fatigue (20%), urinary tract infection (UTI; 17%), back pain (17%), rash (17%), nausea (16%), and neutropenia (16%). Grade ≥3 AEs in ≥5% of patients were neutropenia (14%), pneumonia (6%), and anemia (6%). The most common serious AEs were pneumonia (6%) and UTI (2%). Treatment has been discontinued in 21/122 patients (17%): 13 due to PD (11%; 1 patient developed Richter transformation), 4 due to AE, 2 due to withdrawal of consent, and 1 each due to investigator decision and stem cell transplant. One fatal AE occurred (recurrent squamous cell carcinoma while on study drug; unrelated). AEs of interest included major hemorrhage (hemarthrosis and grade 3 purpura; 2%), bleeding (including

contusion, hematuria, petechia, purpura; 57%), neutropenia (including decreased neutrophil count and febrile neutropenia; 19%), thrombocytopenia (6%), fatigue (20%), headache (23%), atrial fibrillation (3%; 2 grade 3), hypertension (8%), diarrhea (30%; no grade ≥3), secondary malignancies (20%), and arthralgia/myalgia (19%). Of the 120 efficacy-evaluable patients (enrolled at least 3 months prior to data cutoff), 22 were treatment-naïve (TN) and 98 were relapsed/refractory (R/R; Table 2). Based on iwCLL criteria (2008, with 2012 modification for partial response with lymphocytosis [PR-L]), with a median follow-up of 25.1 months, the overall response rate (ORR; PR-L or better) was 97% (116 of 120), complete response rate (CRR; complete response [CR] or CR with incomplete bone marrow recovery [CRi]) was 14%. The ORR was comparable between TN and R/R patients. Median PFS was not reached; PFS rate at 1 year was 97% and at 2 years was 89%. For patients with del(17p), ORR was 94% and CRR was 6%; PFS rate at 2 years was 75%.

**Conclusions:** These data suggest that zanubrutinib monotherapy was generally well tolerated and active in the treatment of patients with CLL/SLL irrespective of 17p deletion status. The ORR, CRR, and 2-year PFS rates suggest this next generation BTK inhibitor can achieve deep and durable responses in patients with CLL/SLL.

**Table 1**. Baseline Characteristics and Adverse Events

| **Patient Characteristics** | **N = 122** |
|---|---|
| Median (range) age, years | 67 (24-87) |
| Eastern Cooperative Oncology Group performance status, n (%) | |
| 0 | 57 (46.7) |
| 1-2 | 65 (53.3) |
| Treatment-naïve, n (%) | 22 (18.0) |
| Relapsed/refractory, n (%) | 100 (82) |
| Median (range) no. prior therapies | 2 (1-10) |
| Bulky Disease, n (%) | |
| Any target lesion LDi >5 cm | |
| Yes | 46 (37.7) |
| No | 76 (62.3) |
| Any target lesion LDi >10 cm | |
| Yes | 4 (3.3) |
| No | 118 (96.7) |
| **Genomic Risk Factors** | |
| del(17p), n (%) | |
| Yes | 16 (13.1) |
| No | 82 (67.2) |
| Unavailable | 24 (19.7) |
| *p53* mutation status, n (%) | |
| Mutated | 13 (10.7) |
| Unmutated | 29 (23.8) |
| Unavailable | 80 (65.6) |
| del(13q), n (%) | |
| Yes | 45 (36.9) |
| No | 52 (42.6) |
| Unavailable | 25 (20.5) |
| del(11q), n (%) | |
| Yes | 22 (18.0) |
| No | 75 (61.5) |

| | |
|---|---|
| Unavailable | 25 (20.5) |
| Trisomy 12, n (%) | |
| Yes | 15 (12.3) |
| No | 81 (66.4) |
| Unavailable | 26 (21.3) |
| IgHV mutation status, n (%) | |
| Mutated | 13 (10.7) |
| Unmutated | 28 (23.0) |
| Unavailable | 81 (66.4) |
| **Adverse events, n (%)** | **N = 122** |
| Any | 121 (99.2) |
| Grade ≥3 | 72 (59.0) |
| Serious | 55 (45.1) |
| Leading to discontinuation | 4 (3.3) |
| Leading to death | 1 (0.8) |

LDi, longest diameter.

**Table 2**. Efficacy: Best Response and 2 Year Progression-free survival estimates

| **Whole cohort** | **TN (n = 22)** | **R/R (n = 98)** | **Overall (n = 120*)** |
|---|---|---|---|
| Median follow-up, months (range) | 27.24 (11.1-42.8) | 20.24 (2.9-47.2) | 25.05 (2.9-47.2) |
| ORR, (PR-L or better), n (%) [95% CI] | 22 (100) [84.6-100.0] | 94 (95.9) [89.9-98.9] | 116 (96.7) [91.7-99.1] |
| CRR, (CR or CRi), n (%) [95% CI] | 3 (13.6) [2.9-34.9] | 14 (14.3) [8.0-22.8] | 17 (14.2) [8.5-21.7] |
| CR, n (%) | 3 (13.6) | 14 (14.3) | 17 (14.2) |
| CRi, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| nPR, n (%) | 0 (0.0) | 1 (1.0) | 1 (0.8) |
| PR, n (%) | 19 (86.4) | 70 (71.4) | 89 (74.2) |
| PR-L, n (%) | 0 (0.0) | 9 (9.2) | 9 (7.5) |
| SD, n (%) | 0 (0.0) | 3 (3.1) | 3 (2.5) |
| PD, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Discontinued prior to first assessment | 0 (0.0) | 1 (1.0) | 1 (0.8) |
| PFS rate at 2 years, % (95% CI) | 95 (71-99) | 88 (76-94) | 89 (80-94) |
| **del(17p)** | **TN (n = 3)** | **R/R (n = 13)** | **Overall (n = 16)** |
| Median follow-up, months (range) | 30.0 (27.0-30.5) | 21.22 (9.4-38.7) | 26.41 (9.4-38.7) |
| ORR, n (%) [95% CI] | 3 (100.0) [29.2-100.0] | 12 (92.3) [64.0-99.8] | 15 (93.8) [69.8-99.8] |
| CRR, n (%) [95% CI] | 0 (0.0) [0.0-70.8] | 1 (7.7) [0.2-36.0] | 1 (6.3) [0.2-30.2] |
| PFS rate at 2 years, % (95% CI) | 100 (NE-NE) | 66 (26-88) | 75 (40-91) |

*120 patients evaluable for efficacy (2 patients non-evaluable as enrolled at least 3 months prior to data cutoff).

CR, complete response; CRi, CR with incomplete bone marrow recovery; CRR, complete response rate; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.