Deep and sustained responses in patients with CLL treated with zanubrutinib or zanubrutinib + obinutuzumab in phase 1/2 AU-003 and phase 1b GA-101 studies: A report from the zanubrutinib extension study

Authors: Constantine S. Tam,[1] Stephen Opat,[2] Eileen Merriman,[3] Jan A. Burger,[4] Emma Verner,[5] Paula Marlton,[6] David J. Gottlieb,[7] Ian W. Flinn,[8] Sumit Madan,[9] Matthew Ku,[10] Radha Prathikanti,[11] Heather Allewelt,[11] Tian Tian,[11] Remus Vezan,[11] Gavin Cull[12]

Affiliations: [1]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [2]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [3]NorthShore Hospital, Auckland, New Zealand; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [6]Princess Alexandra Hospital and University of Queensland, Brisbane, QLD, Australia; [7]Westmead Institute for Medical Research, Sydney, NSW, Australia; [8]Tennessee Oncology/OneOncology, Nashville, TN, USA; [9]Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, AZ, USA; [10]St. Vincent's Hospital, Fitzroy, VIC, Australia; [11]BeiGene USA, Inc, San Mateo, CA, USA; [12]Sir Charles Gairdner Hospital, Nedlands, Australia.

Introduction: The phase 1/2 AU-003 study (BGB-3111-AU-003; NCT02343120) evaluated zanubrutinib monotherapy in patients with various B-cell malignancies, including chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL). The phase 1b GA-101 study (NCT02569476) evaluated zanubrutinib in combination with obinutuzumab (ZO) for 6 cycles followed by continuous zanubrutinib monotherapy in patients with CLL/SLL and follicular lymphoma. At the end of each study, eligible patients could enroll in a long-term extension study, BGB-3111-LTE1 (LTE1, NCT04170283), for continued treatment with zanubrutinib or survival follow-up. Here, we report outcomes in patients with CLL/SLL from AU-003 and GA-101, with extended follow-up from LTE1.

Methods: This ad hoc analysis included all patients with CLL/SLL from AU-003 and GA-101 and incorporated long-term follow-up data for patients who enrolled in LTE1

upon completion of these studies. In LTE1, safety outcomes, including the occurrence of treatment-emergent adverse events (TEAEs), were evaluated at least every 3 months. Investigators assessed disease response at least every 6 months, using modified iWCLL guidelines [CLL: Hallek et al. 2008; SLL: Cheson et al. 2014]; a response category of "*no evidence of progressive disease*" was also available.

Results: In total, 170 patients with CLL/SLL were treated in AU-003 (n=125) and GA-101 (n=45), of whom 117 (AU-003, 84; GA-101, 33) enrolled in LTE1 (108 continued zanubrutinib). At parent study enrollment, median age was 68 years (range, 24-87), and 75.3% had relapsed/refractory (R/R) CLL/SLL, with 1 median prior therapy line (mean, 2; range, 1-10). Del(17p) was present in 17.1% (TN, 19.0%; R/R, 16.4%) and *TP53* mutation in 18.2% of patients (TN, 21.4%; R/R, 17.2%). At LTE1 enrollment, median age was 71 years (range, 40-91) and the median time since zanubrutinib treatment initiation in the parent studies was 44.1 months (range, 20.0-71.6) (TN, 47.9 months; R/R, 40.5 months). As of April 15, 2024, the median follow-up time (parent study + LTE1) was 78.1 months (range, 5.3-106.9) and the median treatment duration was 67.9 months (range, 0.8-106.9). Grade ≥3 and serious TEAEs occurred in 84.1% and 69.4% of patients, respectively. TEAEs led to zanubrutinib and/or obinutuzumab treatment discontinuation in 13.5%, dose reduction in 12.9%, and death in 7.1% (COVID-19, n=2). The prevalence of atrial fibrillation/flutter at >0-3 years, >3-5 years and >5-6 years was 2.9%, 4.0% and 5.4%, and of hypertension was 14.7%, 19.0% and 20.4%, respectively.

In patients receiving zanubrutinib monotherapy (AU-003), with median follow-up of 76 months (range, 5.3-106.9), the overall response rate (ORR; ≥ partial response with lymphocytosis; 95% CI) was 100% (84.6, 100) for TN patients, and 94.2% (87.8, 97.8) for patients with R/R CLL/SLL. The complete response (CR)/CR with incomplete bone marrow recovery (CRi) rate (95% CI) was 36.4% (17.2, 59.3) for TN patients, and 25.2% (17.2, 34.8) for patients with R/R CLL/SLL. COVID-adjusted 72-month event-free rates for progression-free survival (PFS; 95% CI) were 76.2% (51.9, 89.3) for TN patients, and 61.1% (49.8, 70.5) for patients with R/R CLL/SLL. COVID-adjusted 72-month event-free rates for overall survival (OS; 95% CI) were 90.5% (67.0, 97.5) and 81.5% (71.8, 88.1) for patients with TN and R/R CLL, respectively.

In patients receiving ZO (GA-101), with median follow-up of 88.1 months (range, 7.9-98.5), the ORR (95% CI) was 95.6% (84.9, 99.5); the ORR was 100% (83.2, 100) for TN patients and 92.0% (74.0, 99.0) for patients with R/R CLL/SLL. The CR/CRi rate (95% CI) was 60% (36.1, 80.9) for TN patients and 36.0% (18, 57.5) for patients with R/R CLL/SLL. COVID-adjusted 72-month event-free rates for PFS were 78.5% (52.3, 91.4) for TN patients and 44.6% (24.3, 63.2) for patients with R/R CLL/SLL. COVID-adjusted 72-month OS rates were 84.2% (58.7, 94.6) and 63.0% (40.8, 78.8) for patients with TN and R/R CLL, respectively.

Conclusions: Patients with CLL/SLL treated with zanubrutinib monotherapy or ZO for 6 cycles followed by continuous zanubrutinib monotherapy had high rates of overall and complete response, with particularly high CR rates in patients with TN CLL/SLL. With a median follow-up of 6.5 years, the durability of these responses was demonstrated. The tolerability/safety profile of zanubrutinib, alone and in combination with obinutuzumab, remained favorable.