Activity and Tolerability of Ibrutinib in Combination With Ofatumumab in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Samantha M. Jaglowski, MD1, MPH, Jeffrey A. Jones, MD, MPH1, Joseph M. Flynn, DO, MPH1, Leslie A. Andritsos, MD1, Kami J. Maddocks, MD1, Jennifer A. Woyach, MD1, Kristie A. Blum1, MD, Michael R. Grever, MD1, Susan Michelle Geyer, PhD1, Nyla A. Heerema, PhD1, Gerard Lozanski, MD1, Mona Stefoos, BS1, Nathan Hall, MD, PhD1, Veena Nagar, MD1, Brian Munneke, PhD2, Jamie-Sue West2, Jutta K. Neuenburg, MD, PhD2, Danelle F. James, MD, MAS2, Amy J. Johnson, PhD1, John C. Byrd, MD1

1The Ohio State University, Columbus, OH, United States; 2Pharmacyclics, Inc., Sunnyvale, CA, United States

Context: Ibrutinib, a first-in-class, once-daily, oral covalent Bruton’s tyrosine kinase inhibitor, demonstrated significant activity in relapsed/refractory (R/R) CLL. Ofatumumab, an anti-CD20 antibody, has activity in combination with chemotherapy in CLL.

Objective: Evaluate safety and activity of ibrutinib combined with ofatumumab (phase Ib/II) in 3 different sequences.

Patients: Patients with R/R CLL/SLL, PLL, or Richter’s transformation (RT) after ≥2 prior therapies, including a purine analogue.

Intervention: 420 mg oral ibrutinib daily and IV ofatumumab 300/2000 mg (12 doses). Group (G) 1: 1 cycle of ibrutinib, then ofatumumab added; G2: ofatumumab on day (D) 1/cycle (C) 1 and ibrutinib on D2/C1; G3: 2 cycles of ofatumumab, then ibrutinib added on D1/C3.

Results: 71 patients (27, 20, 24 in G1, G2, G3) enrolled; median age 64 years; Rai stage III/IV 61%; 65 had CLL, 1 SLL, 2 PLL, and 3 RT; bulky disease (≥5 cm) in 75%; del(17p) in 44%; del(11q) in 31%. Most frequent AEs included diarrhea (68%), infusion-related reaction (IRR, 45%), peripheral sensory neuropathy (42%), and stomatitis (37%). AEs grade ≥3 occurred in 61%; most common grade 3-4 AE was neutropenia (17%). Serious AEs occurred in 39%, including ≥ grade 3 IRR in 1 patient (G2). AEs led to ibrutinib discontinuation in 6 patients. Nine patients died within 30 days of last dose and 2 within follow-up. ORR in CLL/SLL was 100% in G1, 79% in G2, and 71% in G3. One patient had complete response; 2 additional patients achieved partial response with lymphocytosis. Four patients in G3 progressed before starting ibrutinib. At study end, 52/58 responders (90%) remained progression-free with follow-up of 16, 12, and 11 months for G1, G2, and G3, respectively. The three RT patients had disease control followed by progression on days 471, 168, and 137. At 12 months, PFS was 89%, 85%, and 75% in G1, G2, and G3, respectively; 76% continued ibrutinib in long-term extension study; 2 patients underwent transplant.

Conclusions: Ibrutinib combined with ofatumumab is well tolerated and highly active in R/R CLL/SLL with all 3 dosing sequences. Based on these compelling results, randomized trials evaluating anti-CD20 antibody in combination with ibrutinib are ongoing.