ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib vs ibrutinib in patients with Waldenström macroglobulinemia

Veronique Leblond,[1] Constantine S. Tam,[2] Ramón García-Sanz,[3] Stephen Opat,[4] Shirley D'Sa,[5] Wojciech Jurczak,[6] Hui-Peng Lee,[7] Gavin Cull,[8] Roger G. Owen,[9] Paula Marlton,[10] Bjorn E. Wahlin,[11] Alessandra Tedeschi,[12] Jorge J. Castillo,[13] Tanya Siddiqi,[14] Christian Buske,[15] Wai Y. Chan,[16] Jingjing Schneider,[16] Sheel Patel,[16] Aileen Cohen,[16] and Meletios Dimopoulos[17]

[1]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [2]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [3]Hospital Universitario de Salamanca, Salamanca, Spain; [4]Monash Health, Monash University, Clayton, Victoria, Australia; [5]Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust, London, United Kingdom; [7]Flinders Medical Centre, Adelaide, SA, Australia; [8]Sir Charles Gairdner Hospital, University of Western Australia Perth, WA, Australia; [9]St. James University Hospital, Leeds, United Kingdom; [10]Princess Alexandra Hospital, University of Queensland Brisbane, Queensland, Australia; [11]Karolinska Universitetssjukhuset and Karolinska Institutet, Stockholm, Sweden; [12]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [13]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [14]City Of Hope National Medical Center, Duarte, CA, USA; [15]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [16]BeiGene USA, Inc., San Mateo, CA, USA; and [17]National and Kapodistrian University of Athens, Athens, Greece

Introduction: ASPEN (NCT03053440) is a randomized, open-label, phase 3 study comparing zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor (BTKi) designed to have greater affinity to BTK while minimizing off-target inhibition, with the first-generation BTKi ibrutinib in patients with Waldenström macroglobulinemia (WM). Here we present data with a median follow-up of 43 months.

Methods: Cohort 1 included patients with *MYD88* mutations randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily. Randomization was stratified by *CXCR4* mutational status by Sanger sequencing and lines of prior therapy. Cohort 2 included patients without *MYD88* mutations who received zanubrutinib 160 mg twice daily until progression. The primary endpoint was very good partial response or better (VGPR + complete response [CR] rate).

Results: A total of 201 patients (zanubrutinib arm, n=102; ibrutinib arm, n=99) were enrolled in cohort 1; 28 patients were enrolled in cohort 2. A larger proportion of patients in the zanubrutinib arm of cohort 1 vs ibrutinib had *CXCR4* mutations by next-generation sequencing (32% vs 20%, or 33 of 98 vs 20 of 92 with data available) and were aged >75 years (33% vs 22%). Median duration of treatment was 42 months (zanubrutinib) and 41 months (ibrutinib), with 67% and 58% remaining on treatment, respectively. The VGPR+CR rate by investigator was 36% with zanubrutinib vs 22% with ibrutinib (descriptive $P = 0.02$) in cohort 1, and 31% in cohort 2. One patient achieved CR (cohort 2). In patients with wild type or mutant *CXCR4* from cohort 1, VGPR+CR rates with zanubrutinib vs ibrutinib were 45% vs 28% ($P = 0.04$) and 21% vs 5% ($P = 0.15$), respectively. Median progression-free survival and overall survival were not reached.

Consistent with less off-target inhibition, in cohort 1, rates of atrial fibrillation (7.9% vs 23.5%), diarrhea (21.8% vs 34.7%), hypertension (14.9% vs 25.5%), localized infection (78.2% vs 79.6%), hemorrhage (55.4% vs 62.2%), muscle spasms (10.9% vs 28.6%), pneumonia (5.0% vs 18.4%), and adverse events leading to discontinuation (8.9% vs 19.4%) or death (3.0% vs 5.1%) were lower with zanubrutinib vs ibrutinib, respectively. More patients on ibrutinib experienced cardiovascular AEs, including 1 incidence of ventricular arrhythmia. Neutropenia (including grade ≥3) was higher with zanubrutinib (33.7%) vs ibrutinib (19.4%), although rate of grade ≥3 infection was lower with zanubrutinib (20.8%) vs ibrutinib (27.6%). AE incidence with zanubrutinib was similar across cohorts 1 and 2.

In patients treated with zanubrutinib in cohort 1, hemorrhage, neutropenia and infection prevalence decreased over time. Prevalence of infection was lower in patients treated with zanubrutinib vs ibrutinib. Annual prevalence analysis showed that atrial fibrillation remained ≤5% and hypertension remained stable with zanubrutinib, each with lower prevalence at all intervals vs an increasing trend with ibrutinib.

Consistently, exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanubrutinib vs ibrutinib (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months, respectively; $P < 0.05$).

Conclusions: ASPEN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 months, zanubrutinib was associated with higher VGPR+CR rates and demonstrated clinically meaningful advantages in long-term safety and tolerability vs ibrutinib.