# ASPEN: LONG-TERM FOLLOW-UP RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

**Authors:** Ramon Garcia-Sanz[1]; Constantine S. Tam[2,3,4,5]; Stephen Opat[6]; Shirley D'Sa[7]; Wojciech Jurczak[8]; Hui Lee[9]; Gavin Cull[10]; Roger G. Owen[11]; Paula Marlton[12]; Bjorn E. Wahlin[13]; Alessandra Tedeschi[14]; Jorge J. Castillo[15]; Tanya Siddiqi[16]; Christian Buske[17]; Veronique Leblond[18]; Wai Y. Chan[19]; Jingjing Schneider[19]; Aileen Cohen[19]; and Meletios Dimopoulos[20]

**Affiliations:** [1]Hospital Universitario de Salamanca, Salamanca, Spain;, [2]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [3]University of Melbourne, Parkville, Victoria, Australia; [4]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [5]Royal Melbourne Hospital, Parkville, Victoria, Australia; [6]Monash Health, Monash University, Clayton, Victoria, Australia; [7]Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust, London, United Kingdom; [8]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [9]Flinders Medical Centre, Adelaide, SA, Australia; [10]Sir Charles Gairdner Hospital, University of Western Australia Perth, WA, Australia; [11]St. James University Hospital, Leeds, United Kingdom; [12]Princess Alexandra Hospital, Brisbane, QLD, Australia; [13]Karolinska Universitetssjukhuset and Karolinska Institutet, Stockholm, Sweden; [14]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [15]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [16]City Of Hope National Medical Center, Duarte, CA, USA; [17]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [18]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [19]BeiGene USA, Inc., San Mateo, CA, USA; and [20]National and Kapodistrian University of Athens, Athens, Greece

## ABSTRACT

**Introduction:** ASPEN is a randomized, open-label, phase 3 study comparing zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi, ibrutinib, in WM. Here, data with a median follow-up of 43 months are presented.

**Methods:** In cohort 1, patients with *MYD88* mutations were randomized 1:1 to receive zanubrutinib 160mg twice daily or ibrutinib 420mg once daily; stratification factors were *CXCR4* mutation status and prior lines of therapy. In cohort 2, patients without *MYD88* mutations received zanubrutinib 160mg twice daily. The primary endpoint was the proportion of patients with complete response or very good partial response (CR+VGPR).

**Results:** Cohort 1 enrolled 201 patients (zanubrutinib: n=102; ibrutinib: n=99) and cohort 2 enrolled 28 patients. In total, 24 patients were enrolled across 8 sites in Spain. More cohort 1 patients in the zanubrutinib vs ibrutinib arm had *CXCR4* mutations (32% [33/98] vs 20% [20/92] with next-generation sequencing data) and were aged >75 years (33% vs 22%). With median treatment durations of 42 (zanubrutinib) and 41 (ibrutinib) months, 67% and 58% of patients remain on treatment, respectively. The investigator-assessed CR+VGPR rate was 36% vs 22% for zanubrutinib vs ibrutinib (*P*=.02) in cohort 1 and 31% in cohort 2, which included 1 CR. The CR+VGPR rates for patients with wild-type *CXCR4* were 45% vs 28% (zanubrutinib vs ibrutinib; *P*=.04) and 21% vs 5% (*P*=.15) for patients with mutated *CXCR4*. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, grade ≥3 infection, and adverse events leading to discontinuation/death were lower for zanubrutinib vs ibrutinib, as were exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension (0.2 vs 0.8 and 0.5 vs 1.0 persons/100 person-months; *P*<.05); the neutropenia rate was higher for zanubrutinib. Safety outcomes were similar for zanubrutinib between cohorts.

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