Abstract Title: ASPEN: Results of a phase 3 randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM)

Authors: Meletios Dimopoulos, MD[1]; Stephen Opat, MBBS, FRACP, FRCPA[2,3]; Shirley D'Sa, MD, MRCP, FRCPath[4]; Wojciech Jurczak, MD, PhD[5]; Hui-Peng Lee, MBChB, FRACP, FRCPA[6]; Gavin Cull, MB, BS, FRACP, FRCPA[7,8]; Roger G. Owen, MD[9]; Paula Marlton, MBBS (Hons), FRACP, FRCPA[10]; Björn E. Wahlin, MD, PhD[11]; Ramon Garcia Sanz, MD, PhD[12]; Helen McCarthy, MBBS, PhD[13]; Stephen Mulligan, MBBS, PhD, FRACP, FRCPA[14]; Alessandra Tedeschi, MD[15]; Jorge Castillo, MD[16,17]; Jaroslaw Czyz, MD, PhD[18,19]; Carlos Fernández de Larrea, MD, PhD[20]; David Belada, PhD[21]; Edward Libby, MD[22]; Jeffrey Matous, MD[23]; Marina Motta, MD[24]; Tanya Siddiqi, MD[25]; Monica Tani, MD[26]; Marek Trneny, MD, CSc[27]; Monique Minnema, MD, PhD[28]; Christian Buske, MD[29]; Veronique Leblond, MD[30]; Wai Y. Chan, PhD[31]; Jingjing Schneider, PhD[31]; Aileen Cohen, MD, PhD[31]; Jane Huang, MD,[31]; and Constantine S. Tam, MBBS, MD, FRACP, FRCPA[32,33,34,35]

Affiliations: [1]National and Kapodistrian University of Athens, Athens, Greece; [2]Monash Health, Clayton, Victoria, Australia; [3]Monash University, Clayton, Victoria, Australia; [4]University College London Hospital Foundation Trust, London, United Kingdom; [5]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [6]Flinders Medical Centre, Adelaide, South Australia, Australia; [7]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [8]University of Western Australia, Perth, Western Australia, Australia; [9]St James University Hospital, Leeds, United Kingdom; [10]Princess Alexandra Hospital and University of Queensland, Brisbane, Queensland, Australia; [11]Karolinska Universitetssjukhuset and Karolinska Institutet, Stockholm, Sweden; [12]Hospital Universitario de Salamanca, Salamanca, Spain; [13]Royal Bournemouth and Christchurch Hospital, Bournemouth, United Kingdom; [14]Royal North Shore Hospital, Sydney, New South Wales, Australia; [15]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [16]Dana-Farber Cancer Institute, Boston, MA, USA; [17]Harvard Medical School, Boston, MA, USA; [18]Szpital Uniwersytecki nr 2 im dr. Jana Biziela, Bydgoszcz, Poland; [19]Department of Hematology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland; [20]Hospital Clinic de Barcelona, Barcelona, Spain; [21]FN Hradec Kralove, Hradec Králové, Czech Republic; [22]University of Washington/Seattle Cancer Care Alliance - Clinical Research, Seattle, WA, USA; [23]Colorado Blood Cancer Institute, Denver, CO, USA; [24]AO Spedali Civili di Brescia, Lombardia, Italy; [25]City of Hope National Medical Center, Duarte, CA, USA; [26]Ospedale Civile S.Maria delle Croci, AUSL Ravenna, Ravenna, Italy; [27]Vseobecna fakultni nemocnice v Praze, Prague, Czech Republic; [28]University Medical Center Utrecht, Utrecht, Netherlands; [29]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [30]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [31]BeiGene USA, Inc., San Mateo, CA, USA; [32]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [33]St Vincent's Hospital, Fitzroy, Victoria, Australia; [34]University of Melbourne, Parkville, Victoria, Australia; and [35]Royal Melbourne Hospital, Parkville, Victoria, Australia

Background: Bruton's tyrosine kinase (BTK) inhibition is an emerging standard of care for WM. Zanubrutinib is a potent, specific next-generation BTK inhibitor with higher selectivity for BTK compared with TEC- and EGFR-family kinases, which may be related to off-target toxicities.

Aim/Objective: ASPEN (NCT03053440) is a randomized phase 3 study comparing zanubrutinib, a potent and selective BTK inhibitor, versus ibrutinib, a first generation BTK inhibitor, in patients with WM.

Methods: At ASPEN study entry, *MYD88* gene mutations were assessed by a central laboratory (NeoGenomics). Patients with *MYD88* mutation–positive (*MYD88*$^{mut+}$*)* WM were randomized (1:1) to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily). Patients without *MYD88* mutations were assigned to a separate cohort to receive zanubrutinib; these results are reported separately. Randomization was stratified by *CXCR4* mutational status and prior lines of therapy (0 vs 1-3 vs >3). The primary endpoint was the proportion of patients achieving a complete response or very good partial response (CR+VGPR). Sample size was calculated to provide 81% power to detect a difference in CR+VGPR rate of 35% vs 15% in the subset of patients with relapsed or refractory WM. Primary analysis was planned to occur at ~12 months after the last patient enrolled.

Results: Overall, 201 patients with *MYD88*$^{mut+}$ WM were randomized to receive zanubrutinib (n=102) or ibrutinib (n=99). While the treatment groups were well balanced for most baseline factors, more elderly patients (>75 years, 33.3% vs 22.2%) and more patients with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) were randomized to receive zanubrutinib than ibrutinib. At a median follow-up of 19.4 months, VGPR rate was higher with zanubrutinib than ibrutinib (28.4% vs 19.2%; 2-sided *P*=.09). No complete responses were observed. Rates of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with zanubrutinib compared with ibrutinib. Although the rate of neutropenia was higher with zanubrutinib (29.7% vs 13.3%), grade ≥3 infection rates were similar between treatments (17.8% vs 19.4%).

Conclusions: ASPEN is the largest phase 3 trial of BTK inhibitors in WM and the first head-to-head comparison of BTK inhibitors in any disease. Although not statistically significant, compared with ibrutinib, zanubrutinib was associated with a higher VGPR response rate and demonstrated clinically meaningful advantages in safety and tolerability in patients with *MYD88*$^{mut+}$ WM.