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

Meletios Dimopoulos,[1] Stephen Opat,[2] Shirley D'Sa,[3] Wojciech Jurczak,[4] Hui-Peng Lee,[5] Gavin Cull,[6] Roger G. Owen,[7] Paula Marlton,[8] Bjorn E. Wahlin,[9] Ramon Garcia-Sanz,[10] Helen McCarthy,[11] Stephen Mulligan,[12] Alessandra Tedeschi,[13] Jorge J. Castillo,[14] Jaroslaw Czyz,[15] Carlos Fernandez De Larrea Rodriguez,[16] David Belada,[17] Edward Libby,[18] Jeffrey Matous,[19] Marina Motta,[20] Tanya Siddiqi,[21] Monica Tani,[22] Marek Trneny,[23] Monique Minnema,[24] Christian Buske,[25] Veronique Leblond,[26] Steven P. Treon,[14] Judith Trotman,[27] Wai Y. Chan,[28] Jingjing Schneider,[28] Heather Allewelt,[28] Aileen Cohen,[28] Jane Huang,[28] and Constantine S. Tam[29]

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

Background: ASPEN (NCT03053440) is a randomized, open-label, phase 3 study comparing zanubrutinib, a potent 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 WM. Here we present data with a median follow-up of 43 months.

Aims: To compare the efficacy and safety of zanubrutinib vs ibrutinib in patients with *MYD88* mutant (*MYD88*^{mut}) WM and zanubrutinib in patients with wild-type *MYD88 (MYD88*^{wt}) WM.

Methods: In cohort 1, patients with *MYD88*^{mut} were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily. In cohort 2, patients with *MYD88*^{wt} received zanubrutinib 160 mg twice daily until progression. Randomization was stratified by *CXCR4* mutational status by Sanger

sequencing and lines of prior therapy. The primary endpoint was very good partial response or better (VGPR + complete response [CR] rate).

Results: A total of 201 patients (102 zanubrutinib; 99 ibrutinib) were enrolled in cohort 1 and 28 in cohort 2. Baseline characteristics in cohort 1 differed between patients treated with zanubrutinib vs ibrutinib in *CXCR4* mutations by next-generation sequencing (32% vs 20%, or 33 of 98 vs 20 of 92 available samples, respectively) and patients aged >75 years (33% vs 22%, respectively). Median duration of treatment was 42 (zanubrutinib) and 41 months (ibrutinib), with 67% and 58% of patients 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 in cohort 2 obtained a CR. In cohort 1 patients with $CXCR4^{WT}$ or $CXCR4^{MUT}$, 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 and overall survivals were not reached.

Consistent with less off-target inhibition, rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events (AEs) leading to discontinuation or death were lower with zanubrutinib vs ibrutinib (Table). 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; $P < 0.05$).

Conclusion: 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.

Table

AE (all grade), % of treated patients	Cohort 1 Zanubrutinib (n=101)	Cohort 1 Ibrutinib (n=98)	Cohort 2 Zanubrutinib (n=28)
AE, grade ≥3	74.3	72.4	71.4
AE leading to discontinuation	8.9	19.4	14.3
Atrial fibrillation/flutter[a]	7.9	23.5	7.1
Diarrhea	21.8	34.7	32.1
Hemorrhage[a]	55.4	62.2	39.3
Major bleeding[b]	7.9	12.2	7.1
Hypertension[a]	14.9	25.5	10.7
Muscle spasm	10.9	28.6	14.3
Localized infection	1.0	11.2	7.1
Neutropenia[a]	33.7	19.4	21.4
Pneumonia	5.0	18.4	14.3
Infection,[a] all grade (grade ≥3)	78.2 (20.8)	79.6 (27.6)	82.1 (32.1)

[a]Grouped term.
[b]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.
AE, adverse event.