Title: Updated results of the ASPEN trial from a cohort of patients with *MYD88* wild-type (*MYD88*^{WT}) Waldenström macroglobulinemia (WM)

Authors: Meletios Dimopoulos, MD[1]; Ramon García-Sanz, MD, PhD[2]; Hui-Peng Lee, MBChB, FRACP, FRCPA[3]; Marek Trneny, MD[4]; Marzia Varettoni, MD[5]; Roger G. Owen, MD[6]; Jorge J. Castillo, MD[7,8]; Tanya Siddiqi, MD[9]; Alessandra Tedeschi, MD[10]; Christian Buske, MD[11]; Veronique Leblond, MD[12]; Wai Y. Chan, PhD[13]; Jingjing Schneider, PhD[13]; Sunhee Ro, PhD[13]; Aileen Cohen, MD, PhD[13]; Jane Huang, MD[13]; and Constantine S. Tam, MBBS, MD, FRACP, FRCPA[14,15,16,17]

[1]National and Kapodistrian University of Athens, Athens, Greece; [2]Hospital Universitario de Salamanca, Salamanca, Spain; [3]Flinders Medical Centre, Adelaide, SA, Australia; [4]Charles University General Hospital, Prague, Czech Republic; [5]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [6]St. James University Hospital, Leeds, United Kingdom; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]Harvard Medical School, Boston, MA, USA; [9]City Of Hope National Medical Center, Duarte, CA, USA; [10]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [11]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [12]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [13]BeiGene USA, Inc., San Mateo, CA, USA; [14]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [15]St Vincent's Hospital, Fitzroy, Victoria, Australia; [16]University of Melbourne, Parkville, Victoria, Australia; and [17]Royal Melbourne Hospital, Parkville, Victoria, Australia

Background: Inhibitors of Bruton tyrosine kinase (BTK) have shown significant activity in patients with WM harboring a mutation in the *MYD88* gene. However, lower response rates and shorter progression-free survival have been reported in patients with WM who lack such mutations (*N Engl J Med*. 2015;372:1430). The ASPEN trial evaluated zanubrutinib (ZANU), a potent and selective BTK inhibitor, in WM patients.

Methods: In the ASPEN trial, bone marrow *MYD88* mutations were assessed at study entry by a central laboratory (NeoGenomics). Based on the results of the *MYD88* mutation assay, patients were assigned to cohort 1 (*MYD88* mutation) or cohort 2 (*MYD88*^{WT} or mutation unknown). All cohort 2 patients received ZANU 160 mg twice daily until disease progression. The objective was to assess the safety and efficacy of ZANU in patients with *MYD88*^{WT} WM.

Results: In total, 28 patients with 26 *MYD88*^{WT} WM were enrolled into cohort 2. The median age was 72 years; 5 patients were treatment-naïve (TN) and 23 patients were relapsed/refractory (R/R). With the median follow-up of 17.9 months, 2 patients discontinued ZANU due to adverse events, and 6 patients experienced disease progression. The overall response rate was 80.8%, with a major response rate of 50.0%, including a very good partial response (VGPR) rate of 26.9% (Table). Progression-free survival event-free rate at 12 months was 72.4%. The most frequently reported adverse events (AEs) were diarrhea, anemia, contusion, pyrexia, and upper respiratory tract infection. Major hemorrhage was reported in 2 patients, and atrial fibrillation was reported in 1 patient. There were no fatal AEs.

Conclusions: ZANU showed clinically meaningful antitumor activity, including achieving major responses and durability of responses, and was considered well-tolerated with a low discontinuation rate due to AEs, in patients with *MYD88*^{WT} WM. NCT03053440.

Table.

	TN (n=5)	**R/R (n=21)**	**Overall (n=26)**
Median follow-up, mo	19.3	17.1	17.9
Best Overall Response, n (%)			
Complete response	0	0	0
VGPR	1 (20.0)	6 (28.6)	7 (26.9)
PR	1 (20.0)	5 (23.8)	6 (23.1)
Minor response	2 (40.0)	6 (28.6)	8 (30.8)
Stable disease	1 (20.0)	3 (14.3)	4 (15.4)
Progressive disease	0	1 (4.8)	1 (3.8)